

Cadbury² of the Lingnan University, Canton, said that at a recent meeting of the China Medical Association in Shanghai, in the course of a discussion on cancer among the Chinese, the conclusion was reached that carcinoma of the breast is the most prevalent form, carcinoma of the penis and carcinoma of the cervix uteri, following in that order. This is of course for the whole of China and would indicate that for the whole country the incidence of carcinoma of the liver is not sufficiently increased to compare with those mentioned. Maxwell³ made some interesting comparisons regarding the incidence of malignant disease in Chinese and on this continent. He compared a series of 1,133 cases of cancer as to location of the lesion with a series of 3,163 cases from Chicago (Hoffman). His observations agree with those just mentioned, that the commonest forms of cancer in China are those of the breast, penis and cervix in that order. He pointed out, however, that the carcinomas that are found in China are those that are looked for, and mentioned the fact that at one time he considered carcinoma of the uterus to be rare, but that, after a gynecological clinic was opened, he found this form of carcinoma common. It is of interest to note that these three forms of carcinoma, of the breast, penis and cervix, are external, and would be more easily discovered than the forms that could be disclosed only by careful autopsy. In Maxwell's series carcinoma of the liver and gallbladder was found in only 4 per cent as compared with 8 per cent in Hoffman's series. The absence of any certification as to the cause of death means that many obscure internal disorders will be overlooked. Maxwell mentioned that he knows that carcinoma of the liver is common in certain limited areas where infection with *Clonorchis* is common. Other observations also point to the fact that the incidence of primary carcinoma of the liver seems to coincide with that of infections with *Clonorchis sinensis*.

More pertinent figures for our purposes were obtained from Dr. Berglund,⁴ at that time professor of medicine at the Peiping Union Medical College, who forwarded the following figures from Dr. J. C. Tull, government pathologist in Singapore. During 1926, among 1,312 autopsies there were 23 cases of nodular cirrhosis, 19 instances of syphilitic cirrhosis, 5 cases of biliary cirrhosis, and finally 6 cases of cirrhosis due to *Schistosoma*, making altogether 53 cases of cirrhosis. There were, further, 16 cases of primary carcinoma of the liver, contrasted with only 14 cases of primary carcinoma of the stomach. There is apparently a definitely increased incidence of chronic disease of the liver in southern China. Snijders⁵ also mentioned that the most strik-

2. Cadbury, W. W.: Personal communication to the authors.

3. Maxwell, J. L.: Cancer Among Chinese, China M. J. 42:69, 1928.

4. Berglund: Personal communication to the authors.

5. Snijders: Cancer in the Tropics, China M. J. 38:303, 1924.

ARCHIVES OF INTERNAL MEDICINE

EDITORIAL BOARD .

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston

WARFIELD T. LONGCOPE, Baltimore

GEORGE DOCK, Pasadena, Calif.

WALTER W. PALMER, New York

W. S. THAYER, Baltimore

VOLUME 46
1930

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO

We have given raw meat, in the form of lumps, in amounts as large as 175 Gm. for each kilogram of body weight, and have marveled at the thoroughness with which it was digested. Raw meat was handled better than cooked meat. It seemed to be impossible to break down the ability of the stomach and bowel to handle these large amounts of food, and at no point was there any sudden increase in the percentage of residue excreted. The result of the experiments was different, however, when the meat was given finely ground. In this case, a large increase in the amount fed resulted in an increase in the percentage of undigested residue.

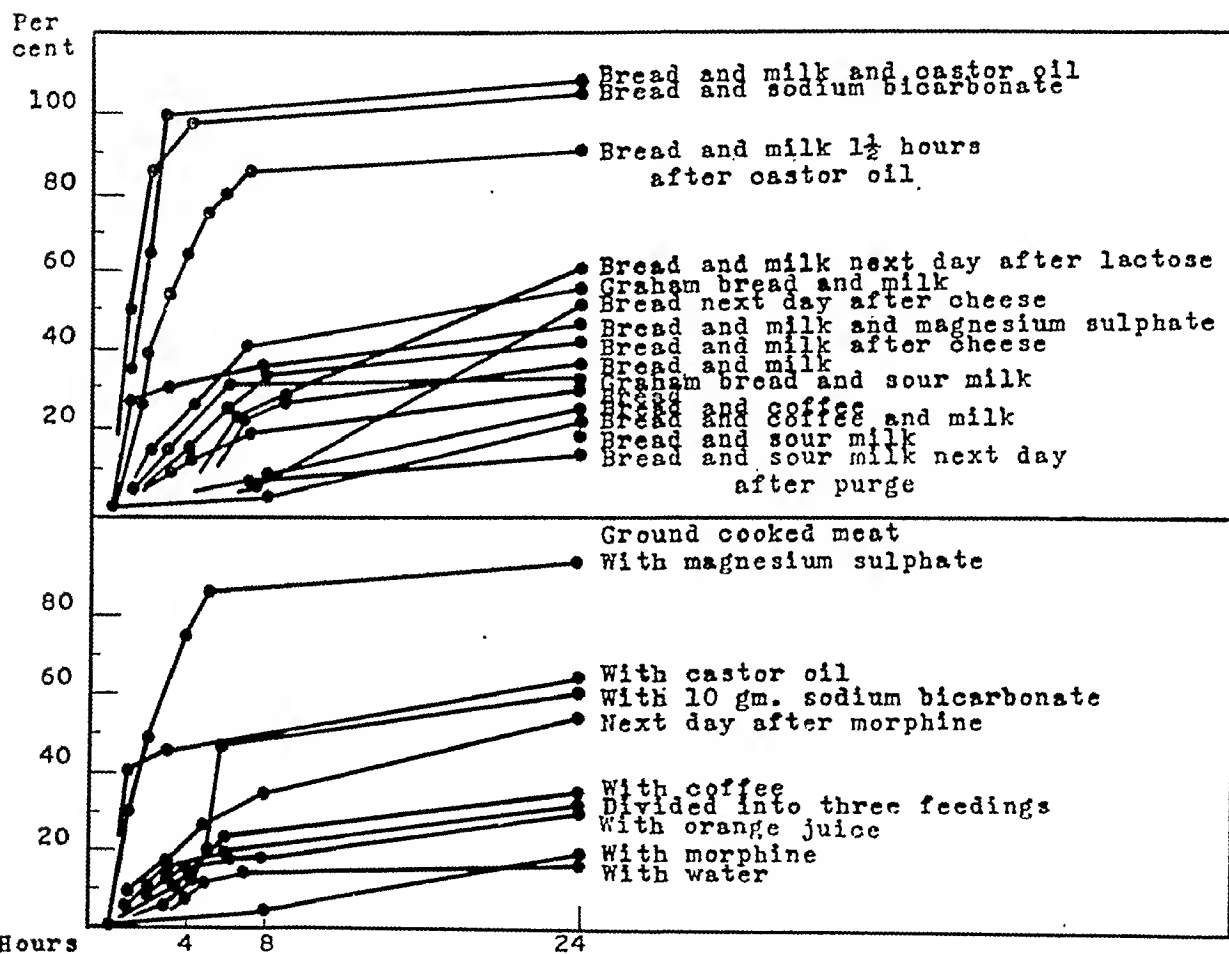


Chart 3.—The digestibility of bread when eaten alone, when eaten with other foods, or after drugs were taken is shown; also the digestibility of meat under different conditions.

Fat.—Hosoi found that with his dogs he could easily reach the limits of digestion of fat. Lard or butter, when given in considerable quantities, always produced large foul-smelling stools. In the experiments here reported, 10 Gm. for each kilogram of body weight appeared to be about as much as the dogs could stand (chart 2). More than this gave rise to vomiting and diarrhea. On a few occasions, however, when the dogs succeeded in retaining lard in amounts as high as 30 Gm. for each kilogram of body weight, it was well digested.

Bateman¹⁰ found that the diarrhea produced by raw white of egg was less severe when the substance was given in divided doses.

Chart 4 shows that when a quantity of food was divided into fractions which were given to the dog at hourly or half-hourly intervals, the residues appeared more promptly than when the total amount was eaten at one time and the percentage undigested was larger. This can be explained by the fact that each successive feeding stimulates peristalsis and gives rise to rush waves which carry the food rapidly down the bowel.

Sodium Bicarbonate.—Ten grams of sodium bicarbonate added to meat or bread increased the amount of residue obtained and increased

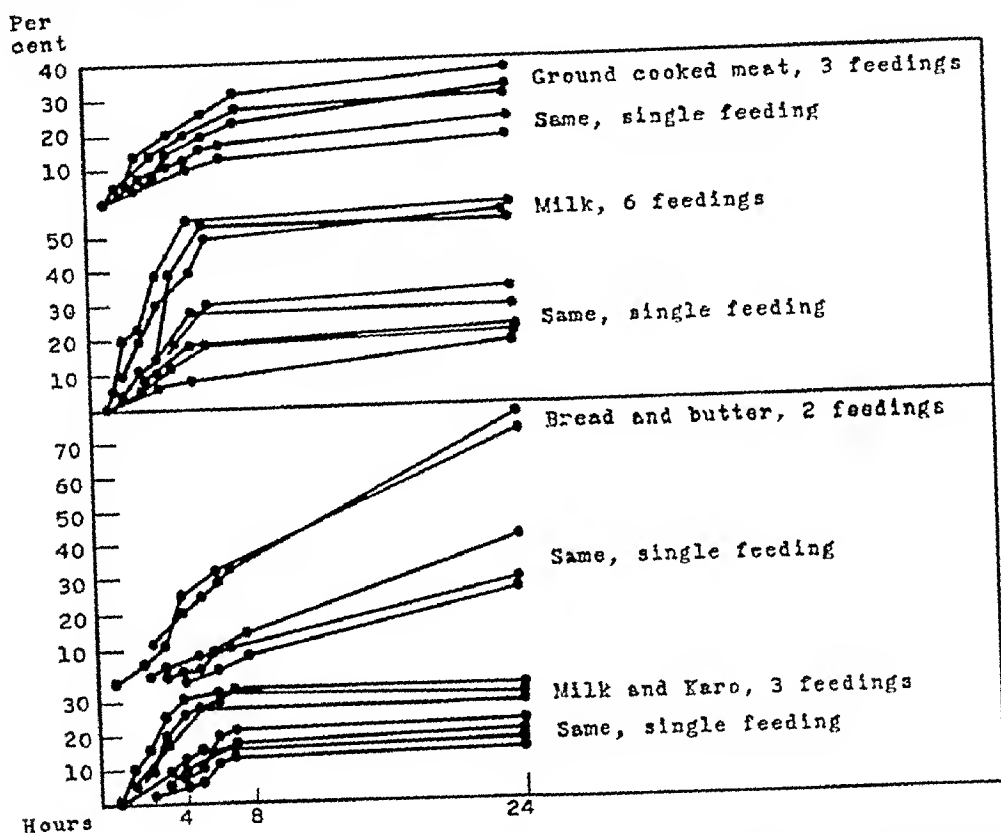


Chart 4.—Difference in digestibility when food was taken in one meal or divided into several portions and eaten at brief intervals.

the content of moisture (chart 3). The dogs became thirsty. The residues were alkaline except in those experiments in which the drug was added to bread and sour milk.

Purgation.—The giving of 30 cc. of castor oil or 17 Gm. of magnesium sulphate two hours before the giving of food always increased the amount of residue obtained. The giving of the purge twenty-four hours before a feeding usually increased the amount of residue obtained from the food (chart 3).

10. Bateman, W. G.: The Digestibility and Utilization of Egg Proteins, J. Biol. Chem. 26:263 (Aug.) 1916.

CONTENTS OF VOLUME 46

JULY, 1930. NUMBER 1

	PAGE
Frequent Chest Colds: Variability in Their Occurrence and the Bacteriology in Those Very Susceptible to This Type of Cold. I. Chandler Walker, M.D., and June Adkinson, A.M., Boston.....	1
Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards: A Statistical Analysis. Walter C. Alvarez, M.D., Rochester, Minn., and L. L. Stanley, M.D., San Quentin, Calif.....	17
The Metabolism of Obesity: VII. The After-Effect of Muscular Exercise on the Production of Basal Heat. Chi Che Wang, Ph.D.; Solomon Strouse, M.D., and Edith Smith, B.S., Chicago.....	40
The Metabolism of Normal and Leukemic Leukocytes. Eugene C. Glover, M.D.; Geneva A. Daland, S.B., and Henry L. Schmitz, M.D., Boston....	46
II. The Diffusible Calcium and the Proteins of the Blood Serum in Malignant Diseases. Lewis Guthrie, M.D., Los Angeles, and David M. Greenberg, Ph.D., Berkeley, Calif., with the Technical Assistance of John B. Dalton.....	67
III. The Diffusible Calcium of the Blood Serum in Allergic Diseases. D. M. Greenberg, Ph.D., Berkeley, Calif., and Lewis Guthrie, M.D., Los Angeles	72
So-Called Malignant Hypertension: A Clinical and Morphologic Study. Francis D. Murphy, M.D., and John Grill, M.D., Milwaukee.....	75
Primary Carcinoma of the Liver. G. F. Strong, M.D., and H. H. Pitts, M.D., Vancouver, Canada.....	105
Chronic Arthritis: Bacteriology of Affected Tissues. Harry M. Margolis, M.D., and Anna H. E. Dorsey, M.S., Rochester, Minn.....	121
Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis. Phillip F. Shapiro, M.D., Chicago.....	137
Book Reviews.....	161

AUGUST, 1930. NUMBER 2

The Value of Acid Neutralization in the Treatment of Gastric and Duodenal Ulcers. Walter Lincoln Palmer, M.D., Chicago.....	165
Laboratory Studies in Epilepsy. Joseph Felsen, M.D., New York.....	180
Bronchial Asthma: The Severe Chronic Intractable Type. I. S. Kahn, M.D., San Antonio, Texas.....	218
Arterial Hypertension: Evaluation of the Prognosis. Edward J. Stieglitz, M.D., Chicago	227
Plasma Proteins. H. J. Wiener, M.D., and R. E. Wiener, Ph.D., New York..	236
Postoperative Results in Toxic Goiter. Norman E. Clarke, M.D., and Irene Black, Detroit.....	266
Postmortem Blood Chemistry in Renal Disease. S. H. Polayes, M.D.; E. Hershey, M.D., and M. Lederer, M.D., Brooklyn.....	283
Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys: I. Concentration of Nonprotein Nitrogenous Constituents in the Blood. A. Maurice Wakeman, M.D., and Clare A. Morrell, M.A., New Haven, Conn.	290
Fatal Human Anaphylactic Shock: Report of a Case, with Autopsy Observations and Review of the Literature. Jesse G. M. Bullowa, M.D., and Mendel Jacobi, M.D., New York.....	306

is an abscess, no harm is done; if it proves to be diphtheria, the hazard to life is not markedly increased by incision. Delayed administration of antitoxin beyond twenty-four hours almost invariably results in death.

CONCURRENT DIPHTHERIA AND ABSCESS

Incision of the fauces in diphtheria cannot often be justified by concurrent presence of diphtheria and quinsy in the same patient. It is true that many patients with diphtheria have at the same time double infection of the throat with diphtheria bacilli and some pyogenic invader. Hemolytic streptococci can be isolated from about one fourth of all diphtheritic throats. Many of the severe cases of diphtheria are actually the result of such double infections, and the cervical lymphadenitis, edema and hyperemia of the fauces are due to the action of pyogenic cocci as much as to the diphtheria bacillus itself. Despite the frequency of such secondary infections, only one instance was noted among 3,260 cases of diphtheria in which peritonsillar abscess was associated with acute diphtheria. The abscess subsided without surgical intervention. Abscess complicated convalescence only three times, always after the disappearance of an extensive membrane, once on the seventh day, once on the tenth day and once on the twenty-first day. In no instance was surgical incision necessary.

CONCLUSIONS

Peritonsillar incision in diphtheria causes an extremely high fatality. It happens through confusion in differentiating faucial diphtheria from quinsy. Adults are most commonly concerned, because diphtheria is usually considered in the differentiation of types of sore throat in children, less commonly in angina of adults. High fever is a valuable symptom in distinguishing pyogenic from diphtheritic sore throat. Bilateral swelling of the fauces should suggest diphtheria; unilateral swelling, peritonsillar abscess, although exceptions are noted.

The necessity for incision of peritonsillar abscess is rarely so urgent that in doubtful cases operation may not be delayed until a culture has been taken to determine whether or not the diphtheria bacillus is present.

Whenever a supposed peritonsillar abscess is incised without delivery of pus, we suggest immediate administration of diphtheria antitoxin. If the condition actually is an abscess, no harm is done; if it proves to be diphtheria, the hazard to life is not markedly increased by incision. Delay in the administration of antitoxin beyond twenty-four hours almost invariably results in death.

CONTENTS OF VOLUME 46

AUGUST—Continued

	PAGE
The Influence of a Special Breakfast on the Basal Metabolism of Patients with a Pathologic Condition. Chi Che Wang, Ph.D., and Jean E. Hawks, M.S., Chicago.....	316
The Intermediate Metabolism of Foreign Sugars. Ella H. Fishberg, M.D., and B. T. Dolin, M.A., New York.....	321
Epigastric Pulsation: Classification in Regard to the Form of the Epigastriogram. Nobutatsu Fukui, M.D., Tokyo, Japan.....	333
Gastric Sequelae of Corrosive Poisoning. William S. Boikan, M.D., and Harry A. Singer, M.D., Chicago.....	342
Book Reviews	358

SEPTEMBER, 1930. NUMBER 3

Digestion: Efficiency with Various Foods and Under Various Conditions. John H. Childrey, M.D.; Walter C. Alvarez, M.D., and Frank C. Mann, M.D., Rochester, Minn.....	361
Addison's Disease in a Negro: Report of a Case. Angelo M. Sala, M.D., and Mendel Jacobi, M.D., New York.....	375
Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys: II. Nitrogen Metabolism. A. Maurice Wakeman, M.D., and Clare A. Morrell, M.A., New Haven, Conn.....	382
The Hazard of Incision for Apparent Quinsy in Diphtheria. J. E. Gordon, Ph.D., M.D., and D. C. Young, M.D., Detroit.....	402
Demonstration of Local Immunity of the Peritoneum by Means of the Shwartzman Phenomenon. Irving A. Frisch, M.D., New York.....	410
Pernicious Anemia: Blood Regeneration During Early Remission. Matthew C. Riddle, M.D., Portland, Ore.....	417
Red Blood Cell Size in Anemia: Its Value in Differential Diagnosis. William P. Murphy, M.D., and Greene Fitzhugh, M.D., Boston.....	440
Iron Metabolism in Pernicious and in Secondary Anemia. Herman H. Riccker, M.D., with the Technical Assistance of Mary E. Winters, B.S., Ann Arbor, Mich.....	458
The Significance of an Electrocardiogram with a Large Q in Lead 3. Harold E. B. Pardee, M.D., New York.....	470
Modification of the Dextrose Tolerance Test as an Index of Metabolic Activity of the Liver. T. L. Althausen, M.D.; Lewis Gunther, M.D.; John B. Lagen, M.D., and William J. Kerr, M.D., San Francisco.....	482
Renal Damage Following Administration of Merbaphen (Novasurol): Report of Nine Cases. Douglas H. Sprunt, M.D., New Haven, Conn.....	494
Transfusion from a Group II (A) Donor to a Group III (B) Recipient Without Fatal Result. Lyman Burnham, M.D., New York.....	502
Parathyroid Tumor and Changes of the Bones. I. Snapper, M.D., Amsterdam, Holland	506
Experimental Gastric Ulcer: The Effect of the Consistency of the Diet on Healing. Gordon B. Fauley, M.D., and A. C. Ivy, M.D., Chicago.....	524
The Life of Reticulocytes: Experiments on Their Maturation. Clark W. Heath, M.D., and Geneva A. Daland, B.S., Boston.....	533
Book Reviews	552

OCTOBER, 1930. NUMBER 4

Resuscitation of the Stopped Heart by Intracardiac Therapy. Albert S. Hyman, M.D., New York.....	553
Diabetes Mellitus. C. A. Mills, M.D., Cincinnati:	
Is Climate a Responsible Factor in the Etiology?.....	569
Sugar Consumption in Its Etiology.....	582

23.6 mg. per hundred cubic centimeters. This unduly high serum calcium content, hypercalcemia, proved to be the principal landmark which led to the correct diagnosis. A more thorough discussion of the general significance of such a hypercalcemia is therefore indicated.

Increase in the serum calcium is rarely met with, while, on the other hand, decreased serum calcium or hypocalcemia, belongs to the characteristic features of tetany, which is caused by damage to the parathyroids.

If, therefore, hypocalcemia is a symptom of impaired function of the parathyroids, hypercalcemia, as observed in this patient with so-called osteomalacia, should point to hyperfunction of the parathyroid.

During the last decade it has become obvious that a connection exists between certain diseases of the skeleton and changes in the morphology and function of the parathyroids; the hypercalcemia in this case, therefore, suggested that possibly a hyperfunction of the parathyroids might be the cause of the disease.

In 1904, Askanazy described a tumor of one parathyroid found in a case of osteitis deformans, after Erdheim had previously discovered an enlargement of these glands in patients suffering from osteomalacia. Since these reports appeared, the number of cases in which a tumor of a parathyroid was found in patients suffering from osteitis fibrosa generalisata has steadily grown. In 1925, Hoffheinz collected from the literature forty-five cases of parathyroid tumor. Of these forty-five patients, twenty-seven suffered from various diseases of the bones, viz., seventeen from osteitis fibrosa generalisata, eight from osteomalacia and two from rachitis. From these observations it has become evident that in all cases of osteitis fibrosa generalisata or Recklinghausen's disease, the possibility of a parathyroid tumor should be borne in mind.

Osteitis fibrosa generalisata is characterized by a fibrous degeneration of the bone, accompanied by the formation of cysts. So-called Recklinghausen's disease, therefore, is usually recognized by multiple foci of cystic degeneration of the bones. These cysts may be filled with brown, semiliquid material, and pseudosarcomatous giant cell growth often occurs in them, especially if they are situated in the distal ends of the long shafts. Clinical observation has proved, however, that these so-called giant cell sarcomas, which are so frequently observed with osteitis fibrosa generalisata, are always benign; biologically, they are not to be looked on as malignant tumors. Severe pain originating from the bone-marrow is seldom lacking, and it complicates the clinical picture of Recklinghausen's disease. Spontaneous fractures are also not infrequent. The anatomic examination proves that this disease is characterized by both too rapid destruction and too rapid construction of bone tissue. The rapid construction, however, gives rise to inferior osteoid bone tissue which does not calcify. In the long run, the normal

OCTOBER—Continued

	PAGE
Blood Platelets: An Improved Indirect Method for Their Enumeration. Isadore Olef, M.D., Boston.....	585
Tropical Sprue: Experience with Thirty-Six Cases. E. A. Baumgartner, M.D., and C. Harvey Jewett, M.D., Clifton Springs, N.Y.....	597
The Arteriovenous Difference in Blood Sugar Content. B. Y. Glassberg, M.D., St. Louis.....	605
The Nature of Graves' Disease. Eli Moschcowitz, M.D., New York.....	610
The Oxygen and Carbon Dioxide Content of Blood from the Internal Jugular and Other Veins. William G. Lennox, M.D., with the Assistance of Erna Leonhardt, Boston	630
Pulmonary Tuberculosis: Treatment in Allergen-Proof Chambers. W. Storm van Leeuwen, Leiden, Holland.....	637
The Specific Effect of Bile Salts on Pneumococci and on Pneumococcus Pneumonia. Edwin E. Ziegler, M.D., Northport, N. Y.....	644
The Appearance Time of T Wave Changes in the Electrocardiogram Following Acute Coronary Occlusion: Reports of Two Cases. Lewis M. Hurxthal, M.D., Boston.....	657
Evaluation of the Expulsion of Enemas as a Criterion of Intestinal Obstruction. Owen H. Wangenstein, M.D., and Reinhold O. Goehl, B.S., Minneapolis	669
Primary Carcinoma of the Lungs with Metastases to the Central Nervous System. Charles Davison, M.D., and William A. Horwitz, M.D., New York.....	680
Peripheral Arterial Disease in Polycythemia Vera. George E. Brown, M.D., and Herbert Z. Giffin, M.D., Rochester, Minn.....	705
Acute Monocytic (Histiocytic) Leukemia: Review of the Literature and Case Reports. William Dameshek, M.D., Boston.....	718

NOVEMBER, 1930. NUMBER 5

Geographic or Climatic Variations in the Death Rate from Pernicious Anemia, Exophthalmic Goiter, Addison's Disease and Angina Pectoris. C. A. Mills, M.D., Cincinnati.....	741
Diabetes Mellitus: The Colloidal Osmotic Pressure of the Blood. I. M. Rabinowitch, M.D., with the Technical Assistance of Miss Mary Beard, Montreal, Canada	752
The Effects of Intravenous Injections of Foreign Protein on Peptic Ulcer. Jacob Meyer, M.D., and Louis B. Kartoon, M.D., Chicago.....	768
The Boltz Test in Urinalysis. Arthur T. Brice, Jr., B.A., Washington, D. C.	778
Antibody Formation in Kala-Azar. H. L. Chung, M.D., and Hobart A. Reimann, M.D., Peiping, China.....	782
Erythrocyte Sedimentation Test in Tuberculosis: A Study of Two Thousand Cases. Andrew L. Banyai, M.D., and Sylvia V. Anderson, B.S., Wauwatosa, Wis.	787
The Action and Excretion of Nitrates. Norman M. Keith, M.D.; Mary Whelan, M.A., and Edwin G. Bannick, M.D., Rochester, Minn.....	797
Peripheral Neuritis Complicated by Massive Collapse of the Lung Following Tonsillectomy. Harold V. Dwyer, M.D., Detroit.....	833
Carcinomatous Degeneration of Polyp of the Stomach: Report of Eight Personal Cases with a Review of Twenty-Four Recorded by Others. T. Grier Miller, M.D.; E. L. Eliason, M.D., and V. W. M. Wright, M.D., Philadelphia	841
Low Basal Metabolism Without Myxedema. Francis M. Thurmon, M.D., Boston, and Willard Owen Thompson, M.D., Chicago.....	879
Book Reviews	898

TROPICAL SPRUE

EXPERIENCE WITH THIRTY-SIX CASES *

E. A. BAUMGARTNER, M.D.

AND

C. HARVEY JEWETT, M.D.

CLIFTON SPRINGS, N. Y.

According to Osler, it is difficult to classify sprue, as various views of its etiology are held. It is a disease of tropical or subtropical countries, more often occurring in the newcomer and in the better class of people. The disease is characterized by a distinctive sore tongue and mouth, a peculiar type of diarrhea, marked anemia, loss of weight and a tendency to remissions and exacerbations. Its etiology is unknown; various theories are given, some of which are pancreatic disease, mold, infection with *Monilia* or bacteria or deficiency in fat.

In this paper we shall deal more especially with the study of sprue as we have found it in thirty-six patients who have entered our clinic in the past five and one-half years. Most of these patients were missionaries, and most of them came from the Orient. There were sixteen patients from China, seven from India, five from Korea, four from the Philippines, two from Porto Rico, one from Costa Rica and one from Persia. Twenty-four of the patients were women, and twelve were men. None of the patients was under 32 years of age, and sixteen were from 40 to 60 years of age. The oldest was 71. All of these patients had been in the Orient or tropical countries from one to thirty-nine years and had contracted the disease after living for from a few months to thirty-eight years in the foreign country. One patient, after seventeen years' residence in the Philippines, returned to this country underweight and anemic, and typical symptoms of sprue with tetany developed three years later. Another patient, one year after returning to this country, developed symptoms of sprue following a severe infection from a spider bite.

Few autopsies on patients with sprue have been reported. Musgrave reported several cases from the Philippines, Rosenfeld one case, and Baumgartner and Thomas one from our clinic.¹ The marked loss of weight was evident in all cases described as well as the large, thin-walled, dilated colon, which in our case was filled with pasty, gray fecal matter from which *Monilia* was readily grown. The serosal linings, especially

* Submitted for publication, Feb. 28, 1930.

1. Baumgartner, E. A., and Thomas, W. S.: A Case of Tropical Sprue with Autopsy, Clifton M. Bull. 11:90, 1925.

CONTENTS OF VOLUME 46

DECEMBER, 1930. NUMBER 6

	PAGE
The Differentiation and Significance of Certain Ophthalmoscopic Pictures in Hypertensive Diseases. Arthur M. Fishberg, M.D., and B. S. Oppenheimer, M.D., New York.....	901
Does Climate Affect the Human Conception Rate? C. A. Mills, M.D., and Mrs. F. A. Senior, Cincinnati.....	921
Vital Capacity in College Women. Abby H. Turner, Ph.D., South Hadley, Mass.:	
I. Standards for Normal Vital Capacity in College Women.....	930
II. A Study of Students with High and Low Vital Capacity.....	938
Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter. Willard Owen Thompson, M.D., Chicago; Albert E. Morris, M.D., Boston, and Phebe K. Thompson, M.D., Chicago.....	946
The Neutral Red Test in Pernicious Anemia. S. J. Cohen, M.D.; M. J. Matzner, Ch.E., M.D., and Irving Gray, M.D., Brooklyn.....	979
The Diagnostic Value of the Sugar Tolerance Curve in Endocrinopathies. B. Y. Glassberg, M.D., St. Louis.....	984
The Reflex Influence of the Colon, Appendix and Gallbladder on the Stomach. Fred M. Smith, M.D., and George H. Miller, M.D., Iowa City.....	988
The Alkaline Tide as a Method of Studying Gastric Acidity. Roger S. Hubbard, Ph.D., Clifton Springs, N. Y.....	994
Metabolism of Obesity: VIII. Basal Metabolism and Insensible Perspiration During a Period of Reducing Weight. Chi Che Wang, Ph.D.; Solomon Strouse, M.D., and Marie Andersch, B.S., Chicago.....	1002
The Origin of Urobilinogen: A Clinical Experiment. I. M. Rabinowitch, M.D., Montreal, Canada.....	1014
The Correlation of Widal's Postdigestive Leukopenia as a Test for Liver Function with the Normal Rhythm of the Leukocytes. Morris Goodman, M.D., and Joseph E. Connery, M.D., New York.....	1018
Sphenopalatine Phenomena: Present Status of Knowledge. Hiram Byrd, M.D., in Collaboration with Wallace Byrd, A.B., Detroit.....	1026
The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse. Charles C. Wolferth, M.D., and Alexander Margolies, M.D., Philadelphia	1039
Serum Treatment for Chronic Ulcerative Colitis. J. Arnold Bargaen, M.D.; Edward C. Rosenow, M.D., and George F. C. Fasting, M.D., Rochester, Minn.	1063
Book Reviews.....	1072

Unless the patients have had several rectal irrigations before coming to the hospital, the administration of an enema will be regularly returned with flatus and feces unless the obstruction is complete and low in the colon. Following repeated enemas, no return of gas or fecal matter will occur when the obstruction is complete and the lower bowel has become completely evacuated. In incomplete obstructions of the bowel gas will continue to be obtained, though often in small amounts. During the time that preparation is being made for operation, we have, on a



Fig. 1.—Roentgenogram of the abdomen of a dog with severed intestinal obstruction after injection of barium sulphate into the distal loop. A portion of the bowel appears to be contracted in spasm.

number of occasions, had flat x-ray films made of the abdomen before and after the administration of enemas to serve as a visual record of what the attendant observes at the patient's bedside. In incomplete obstructions of the small bowel, a diminution of the gaseous collections in the small intestine may be noted with progression into the colon.

It is easily apparent, therefore, that the expulsion of enemas cannot be a safe guide to the presence or absence of interference with the con-

FREQUENT CHEST COLDS

VARIABILITY IN THEIR OCCURRENCE AND THE BACTERIOLOGY IN
THOSE VERY SUSCEPTIBLE TO THIS TYPE OF COLD *

I. CHANDLER WALKER, M.D.

AND

JUNE ADKINSON, A.M.

BOSTON

This paper concerns only persons who were accustomed to have three or more chest colds a year for a number of years, and who were observed at the time of the colds. Data for thirty-one patients are presented in table 1 to illustrate the variability in the occurrence of colds. Of this number, seventeen were normal persons, and the remaining fourteen were subject to asthma when they had a cold. In fifteen of the thirty-one patients, frequent bacteriologic examinations of the sputum were made at the time of a cold in the chest. Eight of this group were normal persons and seven had asthma with their colds; these cases are presented in table 2. All of the thirty-one patients, whether or not they had asthma, were free from symptoms in the interim between the colds in the chest; therefore, so far as this paper is concerned, all might be considered as normal persons who were subject to frequent chest colds.

The bacteriologic examination, stated briefly, was as follows:

Washed masses of thick sputum, which was raised in the early morning and collected in sterile bottles, were shaken in dextrose bouillon and then inoculated into human blood agar which was poured into petri dishes. After the blood agar plates were incubated from twenty-four to thirty-six hours, depending on how rapidly growth took place, they were examined for types of colonies. Numerous colonies were picked off, inoculated into tubes of dextrose bouillon and incubated for twenty-four hours. These bouillon cultures were then examined for different organisms, and those containing streptococci were inoculated into litmus serum waters. Therefore, examination of the blood agar plate revealed the presence or absence of pigment and hemolysis for the various colonies; examination of the dextrose bouillon culture determined the morphology and straining reaction of the organisms, and the litmus serum waters in the case of the streptococci differentiated both the hemolytic and the nonhemolytic strains into eight subgroups or varieties. No attempt was made to identify bacilli except for morphology, pigment, motility

* Submitted for publication, Nov. 25, 1929.

* The patients were observed in private practice; the bacteriologic work was done in the Medical Laboratory of the Peter Bent Brigham Hospital.

tinuity of the bowel. Failure to obtain a return of gas with a second enema usually indicates that the obstruction is complete; return of flatus, however, does not militate against the presence of obstruction. The distal bowel in intestinal obstruction is anatomically and physiologically normal. Why should it not expel gas? Failure to recognize obstruction of the bowel because the occlusion is incomplete is not an infrequent occurrence, but to defer operation deliberately in acute intestinal obstruction because the block is incomplete is a dangerous responsibility.

When this concept of the "blocked bowel" as a criterion of intestinal obstruction is generally appreciated, patients will come to operation considerably earlier. Procrastination until the block in the bowel is

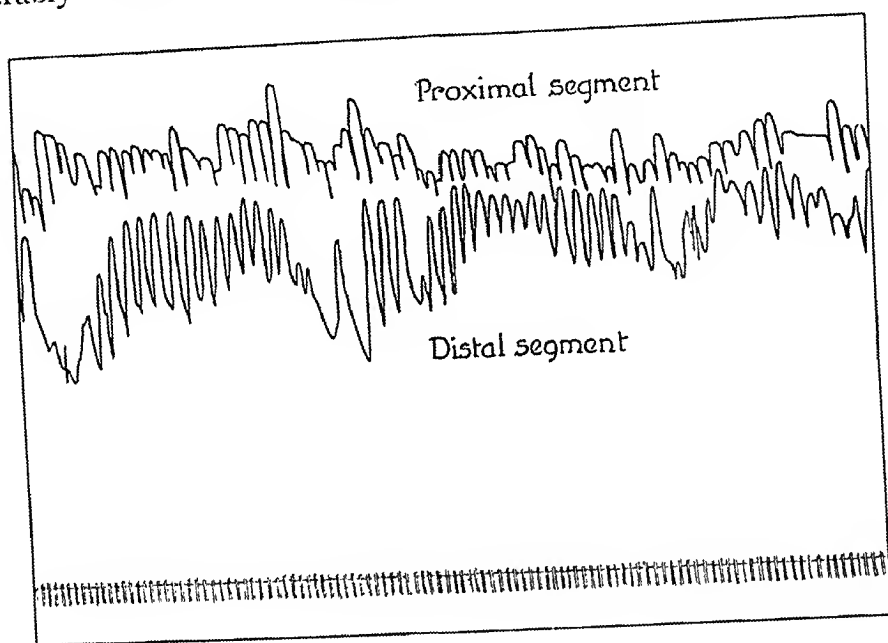


Fig. 4.—Tracing made from a dog with a severed intestinal obstruction of six days' duration. The tracing was obtained under spinal anesthesia. The activity of both the obstructed and unobstructed intestine is great.

absolute is to await confirmation of these signs of obstruction that indicate that precious time and irretrievable opportunity have been lost.

In this communication relative to the employment of enemas as a criterion on which judgment is passed as to the existence of intestinal obstruction, no attempt will be made to elaborate the method of making an early diagnosis. We should like to refer briefly, however, to the criteria on which we believe such an opinion may be arrived at early.

When a mechanical block² exists in the bowel, there are no local physical observations that help to corroborate the suspicion that the

2. Strangulation obstructions in which the blood supply to a portion of the intestine is compromised, however, produce local physical observations.

and staining characteristics. For a more detailed description of the bacteriologic technic, reference may be made to a previous paper.¹

EXPERIMENTAL DATA

In the first column of table 1, a number represents a patient; in the second column, the letter *N* stands for a normal person who had chest colds, and the letter *A* means that the patient had asthma with the chest colds. The remaining columns are headed by figures which denote the various years during which the patient was under observation, and the figures separated by dashes in these columns represent the months

TABLE 1—*Variability of the Occurrence of Colds in Thirty-One Patients*

Patient		1923	1924	1925	1926	1927	1928	1929
1	N	4-10-12	2-4-9-11	2-9-12	3-9-12	4-10-12	1-5-9-12
2	A	3-10-12	2-10-11	2*-10-12	1-3-5-9	3 9-11	4-9-11	3
3	N	1-2-3-5-12	2-5-7-11	1-3-9-12	1-3-5-11-12	1-3-5-10-12	*	...
4	A	3-9-11	4-9-12	3-8-10	11*	4-7-9-12	2-9-12	3-6
5	N	1-3-6-10	2-4-7-11	3-5-6-10	1-4-8-12
6	N	2-8-10	2-5-9-11	2-8-11
7	A	2-4-11	1-4-10	6*	9*	*	1*	...
8	N	3-4-9-11	1*	2*	1-3-5-9	*	3-5-10	.. .
9	N	10*	3-4-5-11	9*	11*	3*	4-10-11	1-3
10	N			1-6-8	1-5-10	5*	3*	*
11	N			3 6-12	3-6-9	*	2-6-7-9	*
12	A				2-4-10-12	3-5-7-9-12	3-7-9-12	3-5
13	N				1-4-9-11	1-5-7-9	1-2-4-9-12	2*
14	A				3-6-9	3-6-12	1-7-10	1*-6
15	A				1-3-10-12	1-4-9-11	3-6-9-11	*
16	A				6-8-10	1-4-9	1-2-3	*
17	N				1-2-3-11	1-9-11	1-2-3-9	1-3
18	N				3-10-12	3-9-10-12	3-6-9	1-4-6
19	N				4-9-11	1-3-12	3-9-10-12	1*
20	A				1-3-8-10	3-4-9	*
21	A				.	2-5-8-10	1-2-6-9-11	3*
22	A					1-5-10	1-3-9-11-12	1-3-6
23	A					2-7-11	2-3-9-11	*
24	N					2-4-9-11	1-2-5-9-12	1-5-7
25	A					3-5-10-12	3-5-10-12	3*
26	A					1-2-7-10	1-3-9-10	*
27	N					2-6-9-11	9*	1*
28	N					.	1-7-9-10	1-4-6
29	A					.	2-4-10-11-12	3-4-6
30	N					.	3-5-9-10-12	1-4-7
31	N					2-7-10	4*

when the patient had a cold; for example, the figure 1 stands for January, 2 for February, 3 for March and so on. The asterisk (*) means that the patient was given preventive treatment against colds during that year.

There would seem to be no need for lengthy discussion of table 1, as all necessary data are presented in it. The first three patients may be taken as an example of all the others. Patient 1, a middle-aged man, was observed for six years, during which time he had twenty colds; there were three colds during each of four years and four colds during each of the other two years. He had a cold in December in

1. Walker, I. Chandler, and Adkinson, June: Bacteriologic Examination of Seven Hundred and Twenty-Four Sputums from as Many Patients with Bronchial Asthma, *Arch. Int. Med.* **41**:601 (April) 1928.

existence of mechanical obstruction. As the fluid and air are carried down toward the point of obstruction by peristaltic rushes, their progress is suddenly arrested, and fluid and air which were intimately mixed in their advance tend to separate as the onward movement is halted. As the air rises to the surface, a sound like drops of water falling in a rain barrel may be heard. The metallic character of the sound has a high pitch imparted by the tension of the dilated intestine. In mechan-



Fig. 6.—Roentgenogram of the abdomen of a dog four and one-half hours after a simple severed intestinal obstruction had been established in the ileum. The gaseous distention of the intestine proximal to the obstruction is apparent.

ical obstruction of the intestine, this metallic tinkle can be detected before the bubble noises referred to are audible. Such sounds may also frequently be heard over the abdomen after an abdominal operation when recovery from the paresis of the intestine incident to the operation begins.

Pain, vomiting, collapse, constipation and meteorism have been the usual standards on which judgment has been based as to whether or not

five of the six years, a cold in September in four of the six years, no cold in June, July or August, and in the other months he had a cold in only one or two years. Patient 2 was a middle-aged woman who had asthma when she had a cold. She had nineteen colds during the six years that she was under observation. During three years she had a cold in each of the months of September, October, November and March; she had no colds in June, July or August, and during one or two years, she had a cold in each of the remaining months. Patient 3, a middle-aged woman, had twenty-three colds in five years. During four years she had colds in each of the months of January, March, May and December; in April, June and August she had no colds, and in the other months she had only one or two colds.

The three patients mentioned lived in the same community; the first and third patients were brother and sister; the second and third were both school teachers; all were practically the same age. The first patient was especially prone to colds during the months of September and December, and the second patient during the months of September, October, November and March; the third patient had most of her colds in January, March, May and December. The first two patients had no colds in June, July and August, and the third patient had one cold in July, but none in April, June or August. In contrast to these three patients, who rarely had colds during the summer months, patients 11 and 14 had colds for several years in June and once in July, and numerous other patients, it is noted, had colds in June, July or August. In other words, some persons who are prone to colds are more apt to have a cold in certain months year after year, other persons have more colds in some other months and still others are more prone to colds in months that are different from either of these. Since all of the thirty-one patients lived within a ten mile radius of Boston, climate, changes in weather, epidemics and exposures would be approximately the same for all in each month. Therefore, the incidence of colds in these cases cannot be correlated very well with these extraneous conditions.

During 1923, eight patients had a total of twenty-eight colds; during 1924, eight patients had the same number of colds, and during 1925 eight patients had two less, so that the same number of patients had practically the same number of colds in each of the three years. During January, May, June, July and August for all three years there was the least number of colds; a total of five colds in any of these months for the three year period was the maximum. Of the other months, during February, March and November there was the largest number of colds, and the months of October and December were a close second, while the months of April and September were next in point of frequency. During 1926, twice as many patients had twice

may be mechanical or inhibitive. In inhibition or paralytic ileus of peritonitis, the stethoscope will reveal a relatively silent abdomen. When the plate is taken in the erect posture, "fluid mirrors" can be made out—concrete evidence of the collection of fluid and gas, affording definite proof of the presence of intestinal stasis.

Lynch and one of us (O. H. W.)⁴ recently put this roentgen evidence of intestinal obstruction to experimental test in the dog. Within four or five hours after the obstruction, definite dilatation of the coils of intestine proximal to the site of intestinal interruption was noted.

In acute intestinal obstruction the administration of barium sulphate is of little help in making an early diagnosis, except in obstructions of the colon or stomach outlet.

Alterations in the blood chemistry are significant of a block high in the intestine but afford no early evidence of intestinal obstruction.

In summarizing briefly the criteria on which an early diagnosis of simple obstruction can be made, it may be said: In a patient complaining of intermittent colicky pain in whom vomiting is usually a prominent feature, but who presents no local physical observations, intestinal obstruction is strongly to be considered. Loud intestinal noises of a metallic character elicited on auscultation of the abdomen lend tenable support to such an impression. The detection of gaseous shadows in the small intestine in the x-ray film adds confirmation and establishes the diagnosis. The continuation of pain despite the return of gas and feces with an enema is indication for immediate operation.

CONCLUSION

The bowel distal to the point of obstruction responds to the injection of enemas much as does the normal intestine. The ability to expel gas and fecal material following the administration of an enema does not militate against the presence of intestinal obstruction.

4. Wangenstein, O. H., and Lynch, F. W.: Evaluation of X-Ray Evidence as Criteria of Intestinal Obstruction, *Proc. Soc. Exper. Med. & Biol.* **27**:674 (April) 1930.

the number of colds. During this year, January and March were the most popular months for colds; September, October and December were the next most popular, but the ratio was nine for the former to six for the latter. During February and the summer months, there was the least number of colds. During 1927, twenty patients had a total of seventy-two colds, and the frequency per month was practically the same as in the previous year, with the exception that September was the leader in frequency. During 1928, twenty-four patients had a total of eighty-eight colds, and again the month of September led in frequency, and January, March, October and December were second in frequency.

On the percentage basis, March led in the frequency of colds; it was among the leaders in frequency for five years. January was among the leaders in three years, February and September in two years and April, October, November and December in one year. January, March and September were most consistent in frequency of colds. It is readily seen, however, that there was wide variance among the months for different years as regards the frequency of colds. In other words, the month of the year had little bearing in general on the frequency of colds, with the exception that during September to May, inclusive, chest colds were more frequent than during the summer period.

The prevalence of epidemics of colds seems to have little bearing on the incidence of chest colds in those very susceptible. Every year during September, when the days are very warm and the nights are frosty in Massachusetts, a large number of colds occur; yet in the cases reported, only in the years 1927 and 1928 did these patients have an unusual number of chest colds. During the past winter, there was an epidemic of colds and influenza in Massachusetts from the middle of December to the middle of January. This group of patients, however, had no greater number of chest colds in December than in the previous January, March and October, nor as many as in the previous September. Furthermore, in January during the epidemic there was no greater number of chest colds in this group than in the following March, and there were fewer colds than in the previous months of January, March, September, October and December. Again the total number of chest colds in this group of cases for December and January, when there was a recognized epidemic, was eighteen, whereas in the previous December and January there was a total of seventeen when there was no general epidemic. Therefore, the presence of epidemics of colds and upper respiratory infections seems to play no part in the incidence of chest colds in very susceptible persons.

It is of interest to consider the incidence of chest colds in this group of cases during the months when there is the least sunshine. March led in the frequency of chest colds in five of the six years under consider-

Laboratory Data.—A roentgenogram of the chest showed small, scattered areas of consolidation throughout all the lobes, suggesting bronchopneumonia. Examination of the skull gave negative results. The spinal fluid showed a positive albumin and globulin content and 40 cells. The Wassermann test of the spinal fluid was negative; that of the blood was four plus.

Death occurred on Oct. 1, 1928.

Diagnosis.—The clinical diagnosis was possible cerebral neoplasm, dementia paralytica and bronchopneumonia. The anatomic diagnosis was carcinoma of the lung, metastases to the lymph nodes of the hilus, brain and pancreas and bronchopneumonia. The microscopic diagnosis was primary papillary carcinoma of the lungs.

Autopsy Observations on the Brain.—The brain was normal in appearance. There were no masses in any areas of the brain, with the exception of an encap-

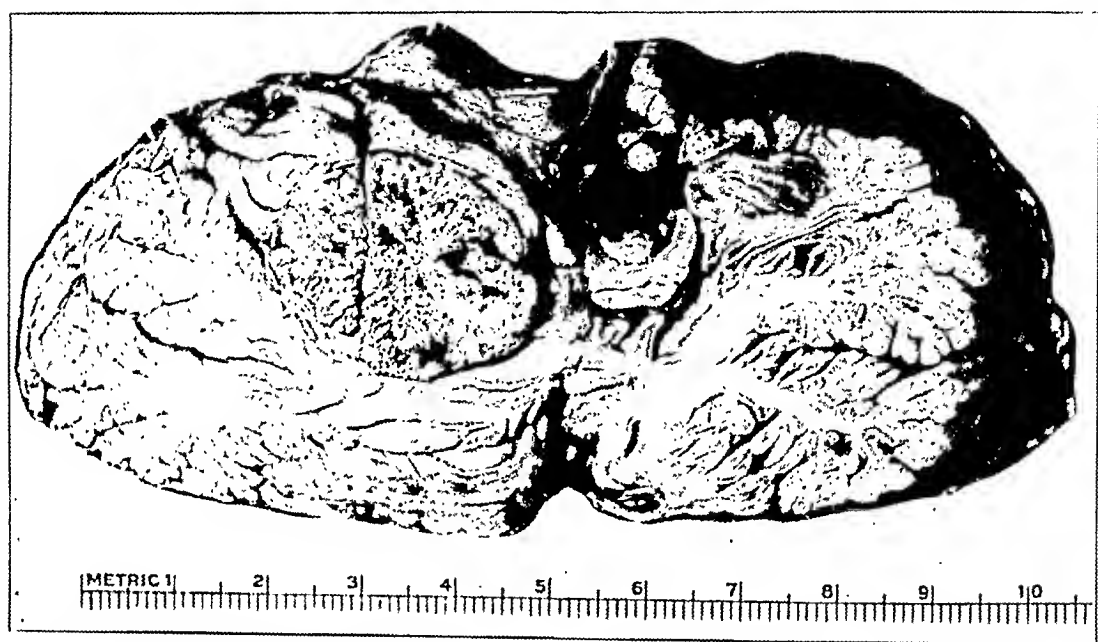


Fig. 7.—Metastatic nodule of the left lobe of the cerebellum.

sulated mass in the region of the right cerebellum, a little larger than a hazelnut (fig. 7). A piece of tissue from the encapsulated mass of the cerebellum showed it to consist of a conglomeration of epithelial cells much like the arrangement of the epithelial cells of the alveolar tissue in the lungs (fig. 8). Numerous mitotic figures were observed.

Sections of the brain were made from various areas and showed a slight thickening of the meninges with a collection of inflammatory cells. The brain tissue proper showed a disturbance of the architectural layers with slight perivascular infiltration within the vessels. There was some proliferation of the capillaries. Numerous rod cells were found. The nerve cells showed various changes, from shrinkage to complete destruction.

The microscopic diagnosis was metastatic carcinoma of the cerebellum (primary, carcinoma of the lung).

The neuropathologic diagnosis was metastatic carcinoma of lung to the cerebellum; dementia paralytica.

ation. During January, a sunless month, there were many chest colds in three years, but in no year was there a larger number of colds than in March of the same year, when there is a good deal of sunlight. February, a month of cold weather and little sun, in comparison, accounted for fewer colds than September, a month of more sun and milder weather. In the month of December, when there is the least sun and much cold, in only one year (1928) was there any appreciable increase in the frequency of chest colds, and even in this instance no more colds were recorded than in January, March, September and October of the same year. During the six years there were nearly as many chest colds in May as in November; yet there is a marked difference in the amount of sun and the degree of cold in these two months. Therefore, with the exception of the months of July and August, when there were very few colds, and of June, when there were fewer colds than during the remainder of the year, the frequency of chest colds in this group of cases cannot be correlated with the absence of sunshine.

The same conclusion is reached if the months of the six year period are grouped according to sunlight. During the months of August, September and October, a total of eighty-one colds was recorded; during the months of November, December and January, there were eighty-eight colds; during the months of February, March and April there were eighty-four colds and during the months of May, June and July there were only forty-four colds. By grouping September, October, March and April together, there is a total of 121 colds, in comparison to 113 colds by grouping together the months of November, December, January and February for the six years.

Consideration of the interval of freedom between colds may throw some light on the cause of frequent colds in the very susceptible person. Excluding the summer period, from June to August inclusive, during which time, as already noted, most patients are free from colds, there were 251 intervals between colds in all of the 31 patients presented in table 1. Of this number, there were forty-two, or nearly 17 per cent, intervals of one month; ninety-two, or 36.5 per cent, intervals of two months; sixty-six, or 26 per cent, intervals of three months; twenty-three, or 9 per cent, intervals of four months, and twenty-eight, or 11 per cent, intervals of five or more months of freedom between colds. In other words, in more than a third of the instances a chest cold occurred two months after the preceding chest cold; and in more than another fourth of the instances a chest cold followed the preceding one in three months; in about one sixth of the instances there was only one month between colds; in less than one tenth of all the interval was four months, and in slightly more than a tenth the total was five or more months.

abdominal lymph nodes, spleen and cerebellum with necrosis; bronchiectasis of the right lung and bronchopneumonia.

Autopsy Observations on the Brain.—The vessels of the brain were markedly congested, especially over the right hemisphere. A slight area of softening involving the tip of the left occipital lobe and left lobe of the cerebellum was noted. On sectioning the brain vertically, the anterior horns of the lateral ventricles were symmetrically enlarged. In the region of the pons on the right side, a gelatinous tumor mass was found which involved the substantia nigra and the pontile fibers (fig. 11). This gelatinous tumor mass was hemorrhagic at the upper and outer borders. Another mass was found involving part of the right cerebellum as well as the vermis (fig. 12). A cavity containing necrotic material was found involving practically the whole side of the left cerebellum.

Sections of the tumor masses in the central nervous system presented the same histologic features as those found in the lung.

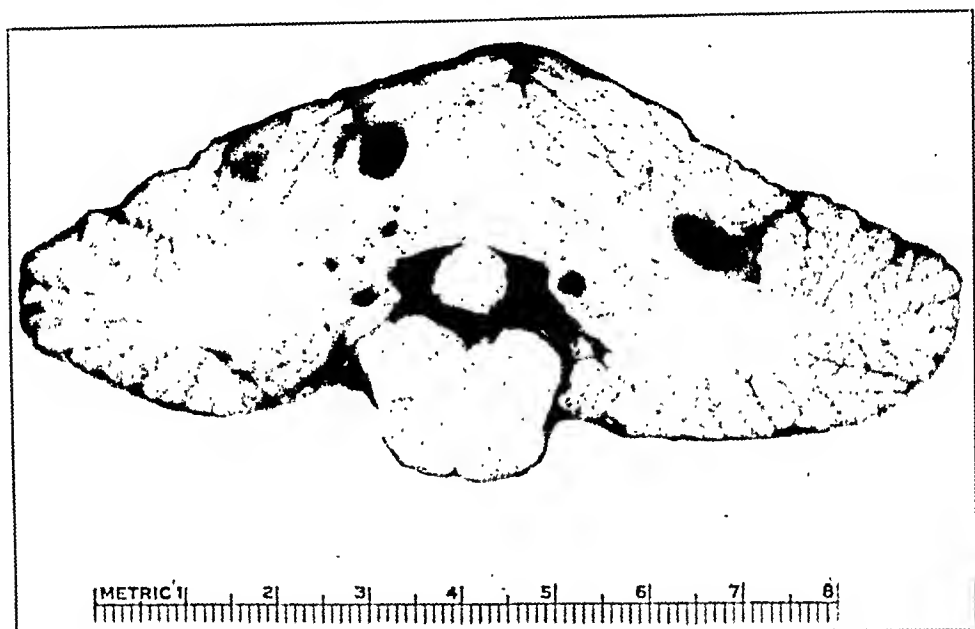


Fig. 10.—Numerous small metastatic nodules to the cerebellum.

Diagnosis.—The condition was diagnosed metastatic adenocarcinoma.

Comment.—The neurologic symptoms came on suddenly about four days prior to death without definite localizing signs. The pulmonary signs antedated the neurologic signs by one year. The histogenesis of the tumor was that of an adenocarcinoma of bronchial origin.

CASE 7.—History.—S. B., a man, aged 61, a jeweler, was admitted to the hospital on July 27, 1929, with the complaints of pain in the back radiating to the left upper extremity, loss of motion in the lower extremities and cough. The patient had had a chronic productive cough for the last thirty to forty years; the expectoration became profuse and blood-streaked eighteen months before admission. In September, 1927, he woke up one morning with intense pain and stiffness of the extremities aggravated by movements of the neck. In May, 1929, he was confined to bed, as he was unable to stand or walk. He noticed paresthesias of the left hand and forearm and frequency in micturition.

In other words, in nearly two thirds of the instances, patients had a cold two or three months after the preceding cold, and in another one sixth the interval was one month. Therefore, as regards the patient, in these cases the immunity established by a chest cold was of short duration. From the standpoint of bacteriology, the cold-causing organisms may be so numerous that some of them cause one cold and others cause the next cold and still others a succeeding cold, so that the frequency of chest colds might be due to these several organisms acting independently and each producing immunity for itself but not for the others rather than from lack of immunity to the same one or more organisms that caused every cold.

Some of these patients were given a curative dose of mixed streptococcus vaccine, as reported in a former paper,² on the second day of their cold, and this treatment seemed to be of benefit in that the cold often rapidly improved and usually disappeared within from one to three days. In other patients, the curative vaccine did not give benefit, and the chest cold continued for two or three weeks. In still others, the chest cold was present for one or two weeks before the curative vaccine was given. As careful a checkup as it is possible to make showed that in these patients the interval of freedom between colds did not seem to be modified whether the patient's cold was of short or of long duration, or whether the patient was treated early or not at all during the cold.

Attention might be directed, incidentally, to those patients who in some years (as evidenced by an asterisk) were given preventive treatment with mixed streptococcus vaccine as already described in a previous paper.³ Exclusive of the year 1929, which was only half finished at the time this article was written, during three yearly periods there were no colds in patients who were accustomed to have three colds a year; in thirteen periods of a year the usual number of three colds was reduced to one, and in four yearly periods the usual number of four or five colds was reduced to one. The year 1929 would seem to bear out similar or better results, since in the period from January to June, inclusive, in five instances in which the usual number of colds had been three or more, there were no colds, and in six other instances the usual number of three or more colds was reduced to one.

In the first column of table 2, the patient is distinguished by a number which refers to the same patient in both tables; in the second column, the letters *N* and *A* refer to the same as in table 1. The third

2. Walker, I. Chandler: Colds and Asthma Associated with Colds: Preventive Treatment with Vaccines, *Arch. Int. Med.* **43**:429 (April) 1929.

3. Walker, I. Chandler: The Curative and Possibly Specific Effect upon Colds of Vaccines Consisting of the Streptococci Prevalent During that Period, *Am. J. M. Sc.* **178**:645 (Nov.) 1929.

denly in four cases, the cerebral signs came on suddenly in all six cases, and the symptoms in the spinal cord came on suddenly in one case. A diagnosis of primary carcinoma of the lung was considered in four of the cases, with the exception of cases 4, 5 and 7. In case 4 a diagnosis of dementia paralytica and bronchopneumonia was made, although a primary neoplasm of the cerebrum was considered as a remote possibility. The predominance of the paretic picture diverted the clinician's attention from the observations on the chest. Histopathologic observations confirmed the diagnosis of dementia paralytica and a metastatic carcinomatous nodule to the cerebellum.

In cases 5 and 7 a diagnosis of chronic fibroid phthisis was made. The neurologic symptoms, with the exception of headache and tinnitus, were negative, and for this reason involvement of the nervous system was not considered. The diagnosis of pulmonary tuberculosis is frequently made instead of primary pulmonary carcinoma of the lung. Occasionally cases are found in which the patients have both tuberculosis and carcinoma of the lung. Cases 3 and 5 fall in this group. Tuberculosis has been considered as a cause of primary carcinoma of the lungs by Ewing⁷ and other investigators. Statistics on the incidence of this occurrence vary to such an extent that one has to be guarded in drawing definite conclusions.

Of the seven cases showing metastases to the central nervous system, three had a single metastasis and three multiple metastases, and one showed a single metastasis causing compression of the spinal cord. Metastases to the cord itself are rare. Simpson¹ found only one case in a series of thirty cases, twenty-nine of which showed involvement of the vertebral column. The occurrence of more than a single metastasis is frequently observed at autopsy. When a single nodule is found, a careful search will reveal other minute nodules (fig. 10). When single metastases occurred, as in cases 3 and 4, these showed involvement of the cervical lymph glands. This induced us to agree with Hassin's view that tumor cells may be carried from the lymph glands of the neck by a backward flow of the lymph along the perineural spaces of some cranial nerves to the subdural or subarachnoid spaces and ultimately to the brain substance. When tumor cells are carried by the blood stream, the likelihood is that the central nervous system will show multiple and not single metastases.

The histogenesis of the tumor in these cases showed them to be bronchial in origin.

In group 2 the ages varied between 47 and 57. The duration of illness was about the same as in group 1. The onset of pulmonary and neurologic symptoms was sudden in cases 1, 2, 3 and 5 and gradual in case 4. The condition in all these cases was diagnosed primary carcinoma of the lung. Two of the cases showed a transverse lesion

column gives the year and the fourth column the month of that year in which a bacteriologic examination of the sputum was made at the time of a cold. In the fifth column, the type of predominating organism is noted; the letters *N.H.* refer to nonhemolytic and the letter *H.* to hemolytic, while the letter *E.* means that both nonhemolytic and hemolytic types of colonies were approximately equal in number. The next eight columns are headed by the names of the eight varieties of hemolytic streptococci, and the second group of eight columns by the names of the eight varieties of nonhemolytic streptococci; the plus sign (+) in these columns means that that variety of streptococcus was recovered from the sputum. Another column is set aside for *Staphylococcus pyogenes-aureus*, and another for bacilli. The last column, which is headed by "Comments," contains several symbols, which are explained as follows. The letter *X* means that only one type of organism, as noted in the table, grew on the agar plate; the letter *Y* means that a few hemolytic colonies were present in the plate but that they did not grow in transplant, and the letter *Z* means that a few nonhemolytic colonies were present in the plate but they did not grow on transplant. Therefore, in these instances these varieties of hemolytic and non-hemolytic organisms could not be identified. The letter *T.* refers to *Micrococcus tetragenus*; the letter *S.* stands for *Sarcinae*; the letters *S.C.* mean *Staphylococcus pyogenes-citreus*, and *S.A.* means *Staphylococcus pyogenes-albus*.

The observations in table 2 are so evident that detailed discussion of all of the patients is unnecessary; a discussion of one patient will suffice. Bacteriologic examination was made of the sputum of patient 17 in 1926, when he had three colds during the three successive months of January, February and March, and with each cold a different type of streptococcus was recovered from the sputum. Eight months later, in November, a still different variety of streptococcus was found. In none of the four examinations was the same variety found twice. From September, 1927, to March, 1928, inclusive, examinations of the sputum were made at the time of five colds. In four successive sputums, nonhemolytic *Streptococcus ignavus* was recovered and in three sputums hemolytic *Streptococcus anginosus*, but four other varieties of streptococci that were found on the first examination were not found subsequently, and in one sputum *Staphylococcus pyogenes-aureus* was recovered. Six months later five varieties of streptococci were recovered, one of which was present six months previously; another was present nearly two years previously and a third was present seven months previously, but the other two varieties had not been recovered before. In January, 1929, or four months after the previous examination, two varieties of streptococci, which were recovered, were present four months previously; another was recovered nearly three years

The effects of treatment in this group of six cases were striking. In every instance, following the administration of phenylhydrazine, and reduction in the total volume of blood, tolerance to exercise increased markedly. In three cases, the clinical symptoms disappeared entirely, and in the remaining three they were markedly improved. Calorimetric studies were carried out in two cases (fig. 1). In these, the rate of elimination of heat was determined by the Stewart-Kegerreis calorimeter. It was found in one case in which the blood volume was 136 cc. for each kilogram of body weight that 0.55 calory was eliminated for each square inch of surface area for each minute of time. Follow-

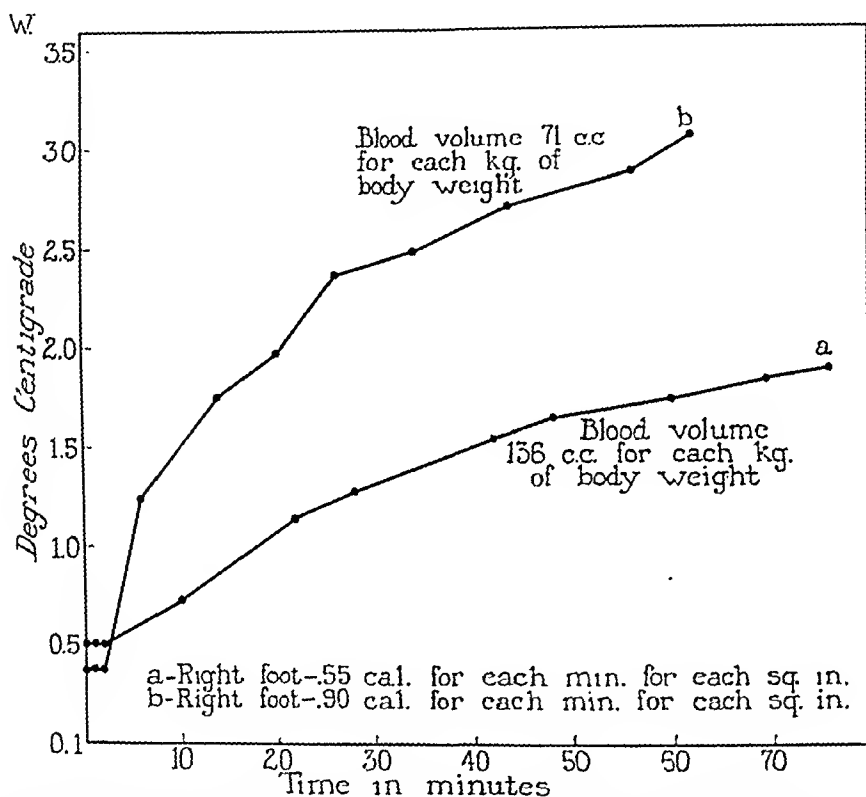


Fig. 1.—The effect of reduction of blood volume on the elimination of heat in arteriosclerosis of the extremities with claudication associated with polycythemia vera.

ing treatment, the blood volume became reduced to 71 cc. for each kilogram of body weight, and the amount of heat eliminated increased to 0.9 calory, with alleviation of the symptoms. The patient was observed for various periods, and it was found that when the blood volume and the concentration of erythrocytes and hemoglobin increased to approximately the levels that had been maintained before treatment, claudication reappeared. A similar study was carried out in a case in which the symptoms were the same as in the one just mentioned. Following treatment, and reduction of the volume of blood, only a slight increase in the rate of elimination of heat was demonstrable, and the symptoms of claudication were not entirely relieved.

TABLE 2.—Results of Bacteriologic Examinations of the Sputum in Fifteen of the Thirty-One Patients

Patient	Year	Month	Predominating Organism	Hemolytic Types						Nonhemolytic Types										Comments			
				Subacidus	Anginosus	Pyogenes	Infrequens	Equi	Hemolytic Type I	Hemolytic Type II	Hemolytic Type III	Ignavus	Salivarius	Fecalis	Mitis	Equinus	Nonhemolytic Type I	Nonhemolytic Type II	Nonhemolytic Type III		Staphylococcus Aureus	Bacillus	
17 N	1926	Jan.	N. H.	+	+
		Feb.	H.	..	+	+
		March	H.	X
		Nov.	H.	+	X
	1927	Sept.	H.	..	+	+
		Nov.	N. H.	+	+	Y
	1928	Jan.	N. H.	+	X
		Feb.	N. H.	..	+	+	..	+
		March	N. H.	+	+	+	..	+	+
		Sept.	H.	+	..	+	+	+	..	+
	1929	Jan.	N. H.	+	..	+	+	+	+
		March	H.	+	+	+	+	+
18 N	1926	Oct.	E.	+	+	+	+
		Dec.	N. H.	+	+	X
	1927	March	E.	+	+
		Sept.	N. H.	+	+	+
		Oct.	H.	+	+	+	+	..	Y
		Dec.	N. H.	+	..	+
	1928	June	N. H.	+	..	+	+	+
		Sept.	H.	+	Z
	1929	Jan.	N. H.	+	..	+	+	Y
		April	N. H.	+	+	+	..	+	+	+
	May	N. H.	..	+	+	+	+	+
		H.	..	+	+	+	+
22 A	1927	March	N. H.	+	X
		Oct.	N. H.	+	X
1 ..	1928	Sept.	H.	+	+	+	Z
		Nov.	N. H.	+	+	+
		Dec.	E.	..	+	+	+
	1929	Jan.	H.	+	Z
March		N. H.	+	+	X	
24 N	1927	Sept.	H.	+	+	+
		Nov.	N. H.	+	..	+	+
	1928	Jan.	N. H.	+	..	+	+
		Feb.	N. H.	+	+	+
		May	N. H.	+	+
		Sept.	H.	Y
		Dec.	H.	..	+	+	+	+
	1929	Jan.	H.	+	..	+	..	+	+	+
29 A		1928	Oct.	H.	Y
	Nov.		H.	..	+	+	+	+	T.S.	
	Dec.		N. H.	+	+	+	..	+	..	+	S.C.	
	1929	March	H.	+	+	+	+	
19 N	1928	Jan.	E.	+	+	+	+	..
		Sept.	N. H.	X
		Oct.	H.	+	+	..	+	+
	1929	Jan.	N. H.	..	+	+	+

REVIEW OF THE LITERATURE

Until Reschad and Schilling-Torgau¹ reported their case in 1913, only two types of leukemia were known: lymphatic and myelogenous. Even as late as 1905, grave doubt existed in the minds of some observers as to the presence of even two types of leukemia. Pinkus,⁷ in 1905, said that "the definition of acute lymphatic leukemia comprehends all the acute leukemia cases so far known. There is no case described without prejudice which shows other than a lymphatic blood-picture or manifests its principal change in any blood-making tissue other than the lymphatic." In Nothnagel's "Encyclopedia of Practical Medicine," in which the foregoing article was written, there is no description of acute myelogenous leukemia, though the chronic form is mentioned.

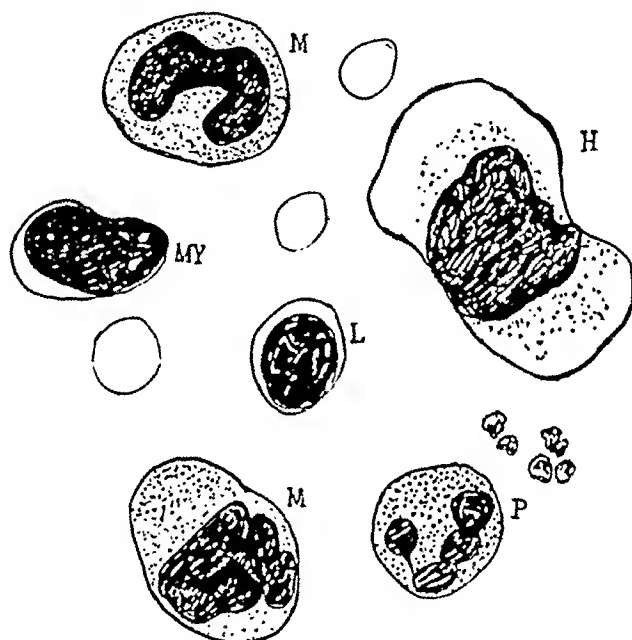


Fig. 1.—These cells are sketched chiefly for purposes of differential diagnosis. Except for the myeloblast (MY) they were seen in one oil immersion field on Oct. 27, 1928. The cells were outlined with a camera lucida; $\times 1,500$. Two typical monocytes (M), a typical histiocyte (H) with a spongy nucleus and characteristic arrangement of granules, a lymphocyte (L) with thick chromatin masses composing the nucleus, a myeloblast (MY) with very fine nuclear meshwork and nucleoli and a polymorphonuclear cell (P) are seen. For further differential points see text.

Since that time, this conception has been almost completely reversed, so that the tendency is now to classify most of the cases of acute leukemia as myelogenous. The possibility is present that some of the cases of acute leukemia classified as lymphatic or myelogenous or unclassified were in reality monocytic in type. The literature will be reviewed briefly in table 3.

7. Pinkus, F.: Acute Lymphatic Leukemia, in Nothnagel: *Encyclopedia of Practical Medicine* (American Edition), Philadelphia, W. B. Saunders Company, 1905, p. 544.

TABLE 14.—*Mineral Metabolism (Case 5)*

Date, 1929		Blood*										Urine										Comment																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																	
		Plasma										Urine																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
		Hemo- globin, rde, Gm. for Each 100 Cc.					Nitrate Carbon Dioxide, Gm. for Each 100 Cc.																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
		Nitro- gen Intake, Gm.	Vol- ume, Cc.	pH	Chloride Gm. N/10	Phosphorus Gm. N/10	Sulphate as Sulphur Trioxide Gm. N/10	Nitrate Nitrogen Gm. N/10	Nitrate- gen Bal- ance, Gm.	Titra- ble Acid- ity, Cc. N/10	Total Fixed Base, Cc. N/10	Ammonia Nitrogen Gm. N/10																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
7/22	0.04	70	

* Specimen of the blood taken before breakfast at end of twenty-four hour period; diet 2, additional daily water 600 cc.
† Given in 25 per cent solution.

before; another was the same as one found nine months previously, and a fifth variety that had not been found previously was recovered. Three months later five varieties of streptococci that had been recovered at some previous time were present and also still another variety that had not been previously recovered. In the four last examinations *Streptococcus hemolyticus-subacidus* was recovered each time, and three other varieties were found repeated once in successive sputums, but of the other varieties that were repeated there were long intervals and one or more colds between repetitions.

During the last two and one-half years, bacteriologic examination of the sputum of patient 17 was made twelve times. The predominating organisms were equally divided between the hemolytic and the non-hemolytic types; in four successive instances each type predominated; in two sputums hemolytic types of streptococci were the only organisms present; in one instance the nonhemolytic type was present alone, and in one specimen, in which both types of colonies were present on the agar plate, no hemolytic colonies grew in subculture. With the exception of one sputum which grew *Staphylococcus pyogenes-aureus* in addition to streptococci, no organism other than streptococci was recovered. In six sputums *Streptococcus ignavus* was recovered; in five sputums, *S. subacidus* and *anginosus*; in four sputums, *nonhemolyticus* type III, and in three sputums, *pyogenes*, *hemolyticus* type III and *salivarius*. *Streptococcus equi*, *hemolyticus* type I, *equinus* and *nonhemolyticus* type I were not found, and the other four varieties were recovered from one sputum.

From one sputum six varieties of streptococci were recovered; from three sputums, five varieties; from two sputums, three varieties, and from the other six sputums, only one or two varieties of streptococci.

Therefore, there is great variability in the types of streptococci that are present in the sputums of patients with chest colds, whether the colds occur at intervals of one or several months. Four or five varieties of streptococci are apt to be present more frequently than some other varieties, provided numerous sputums are examined over a long period of time, but in the same length of time most of the other varieties will be present one or more times. If examinations are confined to some one year or to one or two sputums a year for two or three years, entirely different varieties of streptococci may predominate. For instance, with patient 17 the percentage prevalence of streptococci in the four sputums taken in 1926 is different from that found in the four sputums taken in 1928, and some of the less frequent varieties of streptococci that were present in 1926 were absent in 1928 and vice versa.

Consideration of table 2 as a whole is of interest. Eighty-two bacteriologic examinations were made of as many sputums from the fifteen

temesis, as in our case 7. It accounts chiefly for the symptoms of weakness and dizziness and for the vomiting of blood and the melena.

Such hemorrhage from gastric polyps deserves special consideration, since in certain cases it may be the only lead in arriving at a diagnosis. Furthermore, if a bleeding gastric polyp is not considered in every case of obscure anemia, certain cases will be entirely misdiagnosed. This is strikingly illustrated by the fact that three of our eight cases had been diagnosed originally as primary anemia (cases 1, 6 and 8) by competent internists, one of them eighteen months before a gastric tumor was suspected. In case 7 of our personal series the patient had melena six months before the proper diagnosis was made by roentgenologic study, and even after a profuse hematemesis was allowed to return to work without adequate investigation. Thus it will be seen how these three complications—malignancy, pyloric obstruction and hemorrhage—account for the chief symptoms complained of.

Diarrhea alone is not explained. In our case 5, the patient had this as an initial complaint, and it had been present for six years. She had, in addition to gastric polyps, at least one polyp in the sigmoid, but this could not have caused the diarrhea, which ceased after operation on the stomach. Achlorhydria also may be thought of as an explanation, but again the disappearance of the diarrhea after operation precludes such a possibility. It occurred in two of the cases collected from the literature.

Diagnosis.—In spite of the explanation of the symptoms given, it cannot be claimed that they are sufficiently specific, even when all are present, to lead to a diagnosis. In one of our cases, however, on the basis of the symptoms alone and objective evidence of anemia, such a diagnosis was ventured, and in another case, not reported because the patient has not as yet come to operation, the diagnosis was suggested and subsequent roentgenologic study seemed confirmatory. At least it may be remarked that a middle-aged man suffering irregularly from epigastric distress, anorexia, nausea and vomiting, with blood in the vomitus and feces, achlorhydria and some anemia, should be suspected not only of having carcinoma of the stomach, but of having the special variety under discussion. In this group of data the irregular occurrence of the obstructive phenomena is most suggestive.

The observations of achlorhydria and of blood in the gastric contents lend support to the diagnosis, but do not, of course, differentiate from ordinary mural carcinoma.

The roentgenologic study is the most important means of making the specific diagnosis of a gastric polyp, but does not indicate its malignancy. It was successful in five of our eight cases. The important roentgenologic observations are a characteristic defect and decreased

patients during the two and one-half year period. At least two examinations were made a year of sputum from each patient; in four instances four examinations were made in one year, and in seven instances three examinations were made. From the standpoint of successive examinations, in many instances four and five examinations were made during a seven or eight months' period. In forty-seven examinations nonhemolytic colonies predominated; in twenty-eight examinations hemolytic colonies predominated, and in seven examinations these two types were approximately equal. In only four instances were streptococci not present.

Consideration of the columns headed *Staphylococcus pyogenes-aureus*, Bacilli and "Comments" reveals the following facts. Referring to the letter X, nonhemolytic colonies only were present in fourteen examinations and hemolytic colonies only in two sputums. The letter Y reveals that in eight sputums a few hemolytic colonies were present with many nonhemolytic colonies, but the hemolytic colonies failed to grow in subculture and were therefore not classified. In two sputums both types of colonies were present but failed to grow in subculture. Reference to the letter Z reveals that in three sputums a few nonhemolytic colonies were present together with numerous hemolytic colonies, but in subculture these nonhemolytic organisms did not grow and consequently were not classified. In four sputums from which nonhemolytic colonies only were grown no streptococci were recovered; in two of these sputums, only *Staphylococcus pyogenes-aureus* was recovered, in one only bacilli and in the third both *Staphylococcus pyogenes-aureus* and bacilli.

Of the eighty-two sputums that were plated, in only nine was *Staphylococcus pyogenes-aureus* recovered, in another *Staphylococcus pyogenes-albus*, in two others *Staphylococcus pyogenes-citreus*, in one both *Micrococcus tetragenus* and *sarcinae* and in twelve bacilli. These statistics take into consideration only those plates from which contamination seemed to be eliminated. Naturally, sometimes duplicate plates that were obviously contaminated by bacilli, *Staphylococcus pyogenes-albus* or air organisms were eliminated. Although the types of bacilli were not identified, sufficient study was given to them to determine that none of them were *B. pyocyaneus*, *B. Friedlander*, *B. typhosus*, *B. coli-communis* or *B. subtilis*. It is of interest to note the rare occurrence of the common types of staphylococci, with the exception of *Staphylococcus pyogenes-aureus*, and of the common types of micrococci and diplococci which are supposed normally to frequent the upper respiratory tract.

In comparing the examinations of the first four patients with those of the other patients, the absence of bacilli and of all organisms other than streptococci is noted in the former. This is probably due to the

Sex and Age Incidence.—Consideration of the data presented on these two groups of cases seems to determine, without further comment, that the great majority of the malignant cases occur in the male sex (80 per cent), and that the age incidence is the same as that for the more ordinary variety of gastric carcinoma (83 per cent of our thirty-two patients being over 40 years of age).

Symptomatology.—Uncomplicated benign gastric polyp gives rise to no symptoms, and those presented by these two groups of malignant cases can be explained most satisfactorily on the basis of the three complications originally referred to:

1. The mere presence of a malignant gastric lesion, no matter what its location or conformation, is well known to lead to anorexia, nausea and loss of weight and eventually to emaciation. These phenomena were encountered frequently in our cases and in those reported in the literature.

2. Pyloric obstruction accounts for the pain and the vomiting and incidentally is a factor in the production of anorexia and nausea. It will be noted that these disturbances are often intermittent. This periodicity can be explained by the fact that the polyps, frequently having pedicle attachments in the antral region, are movable in and out of the narrow pyloric canal, thus producing intermittent obstruction. Sometimes they slip through into the duodenal bulb (figs. 1, 3, 7 and 15). In one of our cases (case 4) the polyp was found at operation in the duodenal bulb and could easily be pushed back and forth through the sphincter. The same procedure was carried out at operation in case 7, though the polyp in that instance was originally palpated on the gastric side. In case 3 (fig. 2) the mass could be identified by roentgenologic study in the pyloric antrum.

Pain was present in 70 per cent of the entire series. It was usually referred to as gnawing, crawling or burning; sometimes it was colicky and associated with vomiting. No definite relationship to the intake of food could be determined, although in one instance at least it came on regularly about two hours after eating, thus suggesting a diagnosis of ulcer. Two patients had a sensation of something alive in the stomach, and in both of these the distress was greatest at night, especially when lying on the right side. Relief was obtained by vomiting and by rolling onto the left side. In many cases intervals of complete freedom from distress, lasting days or weeks, were experienced.

3. Hemorrhage is a common occurrence, not only in malignant polyps of the stomach, but also in the benign ones. It may be minute and persistent, as probably in our cases 1 and 8, or profuse with hema-

fact that with the first four patients the specimens of sputum were cultivated within three or four hours after being raised, and the patients were careful about collecting the specimens. The other patients were of the average type and not so particular about the specimens, and often the specimens, although kept cool, were not plated for twenty-four hours.

Variability is noted among the varieties of streptococci in sputums taken from all of the patients collectively during the period of a year or more. By comparison of the more frequently recovered varieties for the years 1927 and 1928, it is found that in 1928 the varieties of *subacidus*, *ignavus* and *salivarius* were recovered much less frequently than in 1927, the variety *infrequens* was much more frequent and the varieties of *anginosus* and nonhemolytic type I were recovered in very nearly the same frequency.

Variability is also noted among the more frequently recovered varieties of streptococci from the individual patient during the period of a year or more. During the period 1926 and 1927, the variety of *subacidus* was recovered once from six sputums of patient 17 and four times in the sputum of patient 18. From seven sputums of patient 22 taken during the years 1927 to 1929, inclusive, *subacidus* was recovered only once, but during the same interval it was recovered four times from the sputum of patient 24. During 1928 and 1929, the same variety of streptococcus was not recovered from four sputums of patients 19, 30, 28 and 23, but it was consistently recovered one or more times from all of the other patients during the same period. The variety *anginosus* was recovered four times from the sputum of patient 17, but not at all from that of patient 18 during the period 1927 to 1929, inclusive. During the period 1926 to 1928, inclusive, the variety *hemolyticus* type I was not recovered from the sputum of patients 17 and 18, but it was recovered from two sputums of patient 22 in 1928. The varieties of *ignavus* and *salivarius* were recovered consistently from some patients, but were not recovered at all from others. During the period 1926 to 1929, inclusive, the variety nonhemolytic type I was not recovered from any of the twelve sputums of patient 17, but during the same period it was recovered from three of eleven sputums of patient 18. Neither was this variety recovered from three other patients, but it was consistently recovered from all of the remaining ten patients.

Variability among the varieties of streptococci recovered from successive sputums obtained from the same patient is similarly noted. First will be discussed those patients whose successive sputums were examined in successive months, and then those whose successive sputum were examined, but in whom a month intervened between colds.

The sputum of patient 17 was examined when he had colds in the successive months of January, February and March in 1926, with the result that of the six varieties of streptococci recovered none occurred

Suprasellar Tumor.—In this case suprasellar tumor was the associated condition.

W. N. (fig. 8), a schoolboy, aged 17, entered the surgical service on Aug. 10, 1926, with definite signs and symptoms of pituitary tumor. A two-stage operation was done. A tumor was found completely burying the optic chiasm. A portion of the tumor was excised. Previous to operation his basal metabolism was minus 24 per cent. He had three roentgen ray exposures of thirty minutes each over the right and left temporal regions (the equivalent of one mild erythema dose) in October, 1926. This was repeated in January, 1927, May, 1928, and May, 1929. In January, 1929, he was a thin, frail boy, easily fatigued, sensitive to cold, and slept most of the time. There were no signs of myxedema. Desiccated thyroid in doses of 3 grains daily raised the basal metabolism from minus 39 to minus 8 per cent and he became irritable, nervous, could not sleep, and at times was

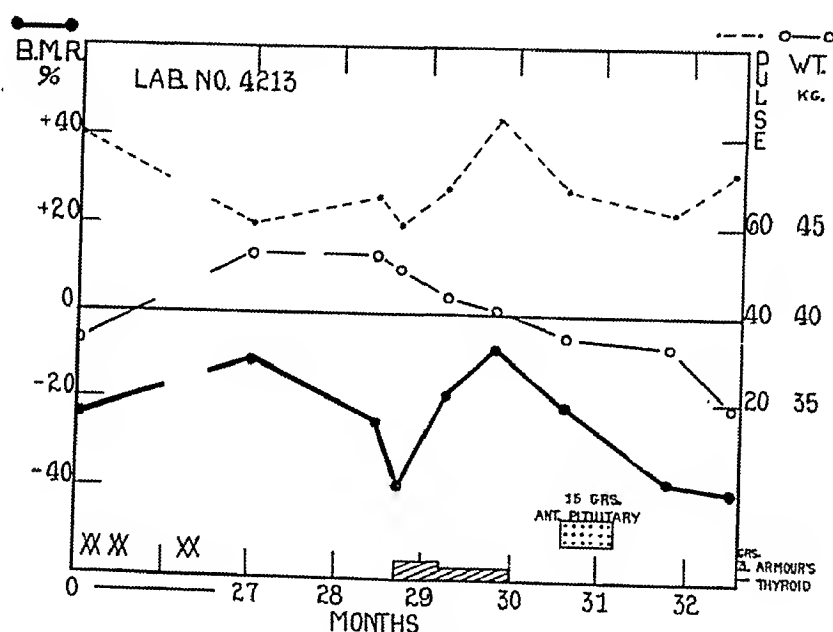


Fig. 8.—Chart of a youth, aged 19, with pituitary tumor in association with loss of weight and a well marked depression of the basal metabolism. Crosses denote roentgen treatment over the pituitary.

incontinent. On omitting thyroid, the metabolism again fell to minus 38 per cent, and he reverted to the torpid state previously noted. Anterior pituitary extract was administered orally in doses of 15 grains daily during the decrease of his basal metabolism, but was discontinued by his mother because she thought it caused increased weakness and anorexia. At the last observation in June, 1929 (three months before death), his basal metabolism was minus 40 per cent.

We have studied two other patients with suprasellar tumor, one with pinealoma, and one with cervical cord tumor, all four of whom showed low basal metabolism.

Multiple Neuritis with Muscular Atrophy.—This was the associated condition in the following case.

twice. In 1928, similar examinations were made in the same months: the variety *ignavus* was recovered from each of the three sputums, and the variety *anginosus* was recovered in two successive sputums, but the third variety in the second sputum did not repeat, and in the third sputum three varieties that had not been recovered in the previous two sputums were present. The sputum of patient 18 was examined in 1927 in September and October and in 1929 in April and May. In the first pair of examinations, two varieties of streptococci repeated and one did not; in the second two successive months, two varieties of streptococci repeated and five did not. Of the sputum of patient 22, three successive examinations were made in November, December and January, with the result that one variety of four repeated in December and one of three in January; in this case, the same variety repeated both times, so that it was present in all three successive sputums. In January and February of 1928, sputums from patient 24 were examined, and none of the three varieties repeated. The same was true with patients 29 and 30; with the former patient, four varieties were present in November, 1928, and five different varieties were present in December, and with the latter patient, the three varieties of streptococci that were present in October were unlike the one that was recovered the previous September.

In other words, in two instances the same variety of streptococcus was recovered from all three sputums taken in three successive months; in three other instances, the same variety repeated the following month; in another three instances, there were no repetitions in the following month, and in one instance, there were no repetitions when three successive sputums were examined in three successive months. Therefore, without further analysis it would seem that those patients whose sputum contained the same organism in two successive months had a very short duration of immunity to these respective organisms. In all instances but one, however, along with the variety that repeated, there were two and often four other varieties, so that the patient may have had immunity to the recurring organisms even though they were in the sputum, and the colds may actually have been caused by other organisms that had not recently been recovered from the sputum. The fact remains, however, that some patients who are prone to chest colds have the same variety of streptococcus with other varieties in their sputum in successive months, while other patients have several different varieties with each successive monthly cold.

The following instances are those of successive examinations of sputum from colds that occurred at intervals of two months; that is, there was a month of freedom between colds. In 1927, the organism recovered from the sputum of patient 17 in November was different from that recovered in September, but during the next cold in January

THE CORRELATION OF WIDAL'S POSTDIGESTIVE LEUKOPENIA AS A TEST FOR LIVER FUNCTION WITH THE NORMAL RHYTHM OF THE LEUKOCYTES *

MORRIS GOODMAN, M.D.

AND

JOSEPH E. CONNERY, M.D.

NEW YORK

Widal, Abrami and Iancovescu¹ described a test for liver dysfunction which they believe is based on an anaphylactic blood reaction. This reaction, to which they gave the name of hemoclastic crisis, manifests itself as (a) leukopenia with a relative lymphocytosis, (b) fall of blood pressure, (c) decrease in the refractometric index of the serum and (d) an increase in the coagulation time of the blood. The authors stated that these phenomena are a response of the presence of low proteins (peptones) in the general circulation. Their theory for the appearance of these products in the general circulation is that during digestion of protein the partially digested proteins which reach the liver via the portal circulation pass through and enter the general circulation when the liver is diseased. The normal liver prevents this transmission, because it has the property of arresting the low proteins (proteopexic function).

These authors offered the following animal experimentation in support of their theory. During digestion of protein either shunting of the portal blood into the systemic circulation by Eck's fistula or the injection of portal blood into a systemic vessel provoked hemoclastic crisis. The authors stated that the leukocyte test for hemoclastic crisis is delicate and definite, and that it will detect liver dysfunction with small quantities of protein. The technic of this test as described by Widal and his collaborators is as follows: The patient fasts for at least five hours preceding the test. A single control white cell count

* Submitted for publication, Feb. 14, 1930.

* From the Department of Medicine, New York University and Third Medical Division, Bellevue Hospital.

* The tests for liver function were carried out by Dr. Norman Jolliffe as a part of his study of liver function (*J. Clin. Investigation* 8:419 [April] 1929).

1. Widal, F.; Abrami, P., and Iancovescu, N.: L'épreuve de l'hémoclasie digestive dans l'étude de l'insuffisance hépatique, *Presse méd.* 28:893 (Dec. 11) 1920.

the same organism that was present in the sputum in November recurred in January. In 1926, patient 18 had different varieties of streptococci in the sputum in October and in December, but in the same months of 1927 two of the three varieties present in October recurred in December. From the sputum of patient 22, none of the four varieties of streptococci that were recovered in September, 1928, was recovered the following November. From the sputum of patient 24, one of the four varieties of streptococci that were recovered from the sputum in September, 1927, was present in the following November, but two months later, in January, none of the four that were present in November recurred. In the case of patient 30, none of the varieties that were recovered from the sputum in October, 1928, was present in December, and the same was true again in February. In the case of patient 25, two of the four varieties that were recovered in October, 1927, were also recovered the following December. Therefore, the observations in this paragraph very nearly duplicate those of the previous one, and similar conclusions are justified, although there was less repetition and more variability among the varieties of streptococci in succeeding sputums.

The difficulties that obtain in making a mixed vaccine of the varieties of streptococci are evident. A combination of all of the sixteen varieties is impracticable, and a combination of the varieties that are encountered most often would still leave out a number of varieties the total of which would comprise an appreciable percentage of frequency. For instance, in the year 1928 forty-eight strains of hemolytic and a like number of nonhemolytic strains were recovered from thirty-seven sputums from the fifteen patients in table 2. A selection of the most frequent varieties of hemolytic streptococci, namely, *subacidus*, *anginosus*, *infrequens* and hemolytic type I would comprise a total of thirty-six of the forty-eight strains that were encountered, and twelve strains distributed among the other four varieties would be omitted. The same procedure applied to the nonhemolytic varieties would mean that thirty-one strains of this type of streptococci would represent three varieties, namely, *ignavus*, *fecalis* and nonhemolytic type I and seventeen strains of this type of streptococcus divided among the five other varieties would be omitted. On consulting table 2 it is found that in a few of the sputums that were obtained at the time of a cold in the chest, only those varieties that are to be omitted from the vaccine were present in the sputum.

SUMMARY

In table 1 are presented data for thirty-one patients who were susceptible to chest colds to the extent of having from three to five a year; seventeen were normal persons and fourteen had asthma with their colds but were well between the attacks of asthma. The cases were

under observation for from two to six years; nine were observed for six years, eleven for four years, seven for three years and four for two years.

Some of the patients had more colds in certain months than did others; other patients had more colds in still other months, and others had colds in months that differed from either of the foregoing. Even those patients who were more prone to colds in certain months evidenced considerable variability in different years, so that in general no particular month seemed to have much bearing on the incidence of chest colds, with the exception that during the summer season there were fewer colds.

Since all of these patients lived within a ten mile radius of Boston, extraneous conditions, such as climate, changes in weather, exposures and epidemics, seemed to have little bearing on the incidence of chest colds in general. Exclusive of the summer season, from June to August inclusive, the incidence of chest colds could not be correlated with the presence or absence of sunshine.

In 17 per cent of all instances the interval between colds was one month, in 36.5 per cent two months, in 26 per cent three months, in 9 per cent four months and in 11 per cent five or more months; in other words, nearly two thirds of the patients had colds every two or three months and another one-sixth had colds within a month of the preceding one. Therefore, in general, these patients seemed to have little immunity to chest colds, and a cold produced only a short immunity, if any, against a succeeding cold.

One treatment with a vaccine at the time of a cold for its curative effect, whether it benefited the cold or not, seemed to have no effect on immunity against the succeeding cold. A series of preventive treatments did seem to produce immunity in that the usual number of colds was reduced from three or more to one or even none for one year in most cases.

In table 2 are presented data for fifteen of the former patients in whom a bacteriologic examination of the sputum was made at the time of a chest cold. Streptococci were isolated from practically all of the eighty-two sputums; from only nine sputums was *Staphylococcus pyogenes-aureus* isolated; from one, *Staphylococcus pyogenes-albus*; from two, *Staphylococcus pyogenes-citreus*; from one, *Micrococcus tetragenous* and *sarcinae*, and from twelve, bacilli. Aside from these organisms no others were isolated, and of the bacilli none was among the common pathologic and easily recognized types.

Among the streptococci there was great variability in the types of hemolytic and nonhemolytic and also great variability among the varieties of each type, whether the colds occurred at intervals of one or several months and whether the examinations were made with

several successive sputums in some one year or with one or two sputums a year for several years. Rarely was the same variety present in three successive sputums.

Varieties of streptococci that were more prevalent in one year were less prevalent than some other variety the next year. Therefore, in order to make a mixed streptococcus vaccine to be used either as a curative or as a preventive in chest colds, constant examination of the sputum in chest colds must be made in order to ascertain the more prevalent varieties. The less prevalent varieties occur fairly often, and occasionally they may be the only organisms that are isolated from the sputum at the time of a cold; therefore, in such instances the vaccine consisting of the more prevalent organisms might be ineffective. However, it would seem to be impracticable to incorporate all sixteen varieties of streptococci into a vaccine.

CONCLUSIONS

There is considerable variability in the occurrence of chest colds in those who are very susceptible, and this seems to be an individual characteristic rather than one due to dependence on extraneous conditions.

Bacteriologic examination of the sputum at the time of a chest cold reveals variability among the varieties of streptococcus, which is the organism most constantly isolated.

For these reasons and since a vaccine consisting of the most prevalent varieties of streptococci seems frequently to prevent and often to benefit a cold in the chest, it is fair to assume that streptococci play a part in the cause of colds.

483 Beacon Street.

BLOOD PRESSURE IN SIX THOUSAND PRISONERS AND FOUR HUNDRED PRISON GUARDS

A STATISTICAL ANALYSIS *

WALTER C. ALVAREZ, M.D.

ROCHESTER, MINN.

AND

L. L. STANLEY, M.D.

SAN QUENTIN, CALIF.

In spite of the large amount of work already done on blood pressure, there is still great need for information in regard to standards of normal. As so often happens in medicine, when physicians first discovered hypertension, they immediately devoted all their efforts to curing it, and only gradually and after many years did they become curious enough to undertake such studies as would enable them to determine when a given pressure represents disease and when it is only a physiologic variation from the average.

Even today there still is great need for a biologic or anthropologic approach to the problem. Figures which are commonly assumed to represent normal or average blood pressure in men and women at various ages are supplied by insurance companies, but these standards are not entirely satisfactory, partly because the original data are so often unreliable, but mainly because the persons measured represent a highly selected group of "accepted risks." It should be obvious that if one decides to accept for insurance only those persons whose blood pressures fall between limits of, let us say, 100 and 140 mm. of mercury, the average is bound to come out about 120 mm. Furthermore, when at the start it was assumed that blood pressure would rise step by step with age, and insurance risks were accepted on that basis, it was foreordained that the means obtained in the different age groups would increase steadily from youth to old age. The fact that enormous numbers of cases are used in the analysis does not improve matters, because the resultant means must still be somewhat artificial. What the insurance companies could do to be more helpful would be to publish percentage distributions and particularly modes representing measurements made on all applicants, accepted and rejected. The mode, which represents the commonest or most typical pressure, will naturally be the measurement of central tendency least affected by errors in sampling or by the inclusion in the group studied of many persons with hypertension.

* Submitted for publication, Nov. 12, 1929.

* From the Division of Medicine, the Mayo Clinic.

What is needed is more information secured from the measurement of men and women chosen at random. But how is this to be done, and where can one find subjects suitable for study? Probably the best standards of blood pressure published so far have come out of those university infirmaries in which the incoming freshmen are put through a physical examination (Lee,¹ Barach and Marks,² Alvarez,³ Diehl and Sutherland,⁴ Burlage,⁵ Jackson⁶). Unfortunately, most of these students fall between age limits of 18 and 25 years, so the problem remains of finding unselected groups of men and women older than 25.

While puzzling over this difficulty, it occurred to us that it might be well to take advantage of the opportunity that is offered in many places to study the blood pressure of men confined in state prisons. To be sure, these men have been selected, but the criteria were moral, social, financial and political; that is, the prisoners had broken some of the rules of society, they were caught, and they failed in their efforts to escape punishment. The essential point is that there was no selection along physical lines. Fortunately for our purpose, modern anthropologic research has already shown that Lombroso was wrong, and that in their bodily measurements prisoners are no different from their brethren outside the walls (Brasol⁷).

Another possible advantage of studying blood pressure in prisoners may be found in the fact that they have been freed from the hurry and strain and fatigue incident to earning a living. To a certain extent they are under basal conditions (Addis⁸). The disadvantage of this is, of course, that the figures obtained may not be exactly comparable with

1. Lee, R. I.: Blood Pressure Determinations, Urinary Findings and Differential Blood Counts in a Group of 662 Young Male Adults, Boston M. & S. J. **173**:541, 1915.

2. Barach, J. H., and Marks, W. L.: Blood Pressures, Their Relation to Each Other and to Physical Efficiency, Arch. Int. Med. **13**:648 (April) 1914.

3. Alvarez, W. C.: Blood Pressure in University Freshmen and Office Patients, Arch. Int. Med. **26**:381 (Oct.) 1920; Blood Pressures in Fifteen Thousand University Freshmen, *ibid.* **32**:17 (July) 1923.

4. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men Including a Special Study of Those with Hypertension, Arch. Int. Med. **36**:151 (Aug.) 1925.

5. Burlage, S. R.: The Blood Pressures and Heart Rate in Girls During Adolescence. A Statistical Study of 1,700 Cases, Am. J. Physiol. **64**:252, 1923.

6. Jackson, C. M.: The Physique of Male Students at the University of Minnesota: A Study in Constitutional Anatomy and Physiology, Am. J. Anat. **40**:59, 1927; Physical Measurements of the Female Students at the University of Minnesota, with Special Reference to Body Build and Vital Capacity, Am. J. Phys. Anthropol. **12**:363, 1929.

7. Brasol, Boris: Anthropology and Criminology, Am. J. Phys. Anthropol. **12**:339, 1928.

8. Addis, Thomas: Blood Pressure and Pulse Rate Levels, Arch. Int. Med. **29**:539 (April) 1922.

those secured in the world at large; what is wanted is a standard of normal for men as the physician sees them, hard at work.

During the progress of the study here reported, an effort was made to have the men quiet and rested when the pressures were taken. Within a few days after their arrival the prisoners were called to the hospital, usually on Monday mornings or Friday afternoons. After sitting and waiting for an hour they were called in squads of ten or twelve into a room where they undressed to the waist. Their vision was first tested, and then the blood pressure was measured (with the subject standing). If it was found to be high, the measurement was repeated after an hour. Few of the men evinced more than a mild interest in the proceeding. As will be seen later when we come to discuss the measurements on guards, this apathy probably had an influence on the results. The guards were worried for fear something would be found which would interfere with their being employed, and this may account to some extent for the fact that their pressures were higher than those of the prisoners.

The measurements were all made by O'Neil, a well trained hospital orderly who took a keen interest in the work. A mercury manometer was used, and the readings were made in the usual way with a stethoscope.

THE RANGE AND CENTRAL TENDENCIES OF SYSTOLIC BLOOD PRESSURE AT DIFFERENT AGES

Tables 1, 2, 3 and 4, and charts 1 and 2 summarize the measurements made on 5,364 white prisoners. Of these 3,677 were of normal weight, according to O. H. Roger's New York Life standard table; 1,200 were 11 per cent or more overweight and 487 were 11 per cent or more underweight.

Chart 1 shows graphically how the blood pressure varies with age. The striking feature of these percentage distributions is that the mode or peak remains on the same abscissal line in all the polygons. In other words, in this group of prisoners, a few begin to show hypertension during early and middle life, but most of them reach middle life or old age with pressures no greater than those which they probably had in youth. In the group aged from 40 to 45 years, there begin to appear a number of persons with pressures of 140 mm. or more, but this increase in the incidence of hypertension is not marked until after the age of 50. The failure of the modal or most typical pressure to increase in the first five decades of life is shown also in chart 2. There we have plotted the calculated modes which correspond closely to those which can be located by inspection of the distributions.

We again emphasize the fact that it is this mode which should be of the greatest interest to clinicians when, as so often happens, they wish

TABLE 1.—Systolic Blood Pressure of White Prisoners with Weight Within 10 Per Cent of Normal Average
(Mexicans Are Excluded, Syphilitic Prisoners Are Included)

Pressure in Millimeters	Age, Years																			Per cent- age	Cumul- ated Per- cent- age	Pres- sure in Milli- meters
	15-18	19	20	21	22	23	24	25	26	27	28	29	30-31	32-33	34-35	36-37	38-39	40-44	45-49	50-59	60-64	Total
80-89.....	3	1	2	1	1	1	3	2	..	2	1	17
90-99.....	7	20	12	13	17	8	17	6	11	5	2	6	14	14	5	11	7	12	7	11	..	205
100-109.....	24	51	43	60	74	62	59	43	49	36	36	30	48	42	36	24	33	33	22	15	5	825
110-119.....	36	56	62	75	87	83	63	58	53	66	48	41	59	63	65	39	36	53	45	31	13	1132
120-129.....	28	34	53	55	75	54	64	46	41	44	43	19	50	66	38	27	24	47	29	23	11	871
130-139.....	11	26	27	22	30	16	22	27	13	19	12	9	24	24	15	12	15	28	15	20	8	395
140-149.....	4	2	10	8	7	8	7	1	6	8	3	5	6	7	7	8	3	14	13	17	6	150
150-159.....	1	1	1	2	2	2	4	1	..	4	3	..	3	1	2	..	1	4	4	10	8	54
160-169.....	3	2	..	2	..	1	..	1	1	..	1	..	1	4	2	18
170-179.....	1	1	..	3	5
180-189.....	1	1	2
190-199.....	1	1	2
200-209.....
210-219.....
220-229.....
Total.....	111	190	212	236	297	235	237	185	173	183	148	111	205	218	172	123	120	194	137	132	65	3677
Mean.....	117.5	115.3	118.4	116.8	117.2	117.1	117.5	118.2	115.8	119.4	118.0	116.4	117.8	118.0	117.8	116.9	117.1	120.4	120.9	126.0	135.5	118.3
Standard deviation.....	12.3	12.6	13.9	12.4	13.1	12.3	13.6	12.4	11.5	12.8	11.8	12.6	13.3	12.3	12.9	13.6	13.1	14.9	15.2	19.1	23.8	13.8
Probable error of the mean	0.8	0.6	0.6	0.5	0.5	0.5	0.6	0.6	0.6	0.6	0.7	0.8	0.6	0.6	0.7	0.8	0.8	0.7	0.9	1.1	2.1	0.2
Median.....	116.9	114.3	117.7	115.9	116.4	115.8	116.8	117.3	115.0	117.6	117.3	114.7	116.9	118.3	116.5	116.3	115.6	119.4	118.6	123.9	130.0	117.0
Mode.....	115.7	112.0	116.3	114.1	114.8	113.2	115.0	115.5	113.7	113.4	115.9	111.3	115.1	118.9	113.9	115.4	112.6	117.4	114.3	119.7	119.0	114.4
Coefficient of variation....	10.5	10.9	11.7	10.5	11.2	10.5	11.6	10.5	9.9	10.7	10.0	10.8	11.3	10.4	11.0	11.7	11.2	12.3	12.6	15.1	17.6	11.7
Percentage above 140 mm....	4.5	1.6	5.7	4.2	4.0	5.1	5.1	2.2	3.5	7.1	4.1	5.4	4.9	3.7	5.8	6.5	4.2	9.8	13.1	24.3	36.2	6.3

TABLE 2.—Systolic Blood Pressure of White Prisoners with Weight 11 Per Cent or More Above Normal
(Mexicans Are Excluded, Syphilitic Prisoners Are Included)

Pressure in Millimeters	Age, Years																	Per cent		Cumulative Per- cent			
	15-18	19	20	21	22	23	24	25	26	27	28	29	30-31	32-33	34-35	36-37	38-39	40-44	45-49		50-59	60-84	Total
80-89	..	6	..	1	1	1	1	1	5	0.42
90-99	..	13	4	4	3	2	6	2	2	3	2	59	4.92
100-109	21	30	21	26	9	18	17	15	9	12	13	4	6	10	7	9	10	3	4	3	2	253	21.11
110-119	..	33	18	28	29	29	23	19	22	22	6	10	20	14	8	10	10	15	7	5	1	346	28.82
120-129	11	19	24	24	25	20	17	21	7	11	11	11	14	11	5	6	12	9	5	6	1	270	22.50
130-139	5	12	7	6	16	15	3	11	5	10	7	4	7	8	6	3	3	13	7	5	3	159	13.25
140-149	..	2	3	7	4	6	2	1	2	7	3	2	3	7	3	7	6	8	1	76	6.33
150-159	..	1	1	2	1	..	4	1	1	1	..	2	4	1	19	1.58
160-169	..	2	1	..	1	2	1	1	1	1	10	0.83
170-179	1	1	0.05
180-189
190-199	1	..	1	0.08
200-209
210-219
220-229
230-239
240-249
250-259
260-269
270-279	1	1	0.05
Total	61	88	88	93	110	88	66	69	55	65	43	33	52	53	30	29	36	59	35	36	11	1200	100.00
Mean	114.3	119.3	117.0	118.6	117.7	120.7	116.5	118.9	118.3	120.1	118.3	120.2	121.3	124.8	115.3	115.3	123.9	123.6	126.1	131.7	145.0	119.9	
Median	112.9	117.6	115.6	117.5	116.9	119.0	115.7	119.5	115.9	118.2	120.0	120.9	119.5	122.7	115.0	115.0	123.3	122.2	128.0	132.0	133.3	118.2	
Mode	110.1	114.2	112.8	115.3	115.3	115.6	114.1	120.7	111.1	114.4	123.4	122.3	115.9	118.5	114.4	114.4	122.1	119.4	131.8	132.6	109.9	114.8	

* If the 270 reading is omitted the mean is 132.0 mm.

TABLE 3.—*Systolic Blood Pressure of White Prisoners with Weight 11 Per Cent or More Under Normal (Mexicans are Excluded, Syphilitic Prisoners are Included)*

Pressure in Millimeters	Age, Years					Total	Per Cent	Cumulative Percentage
	15-24	25-29	30-39	40-49	50-84			
80-89.....	..	3	1	2	3	9	1.85	1.85
90-99.....	9	8	21	17	3	58	11.91	13.76
100-109.....	22	13	51	24	5	115	23.61	37.37
110-119.....	14	17	38	29	20	118	24.24	61.61
120-129.....	13	16	26	22	17	94	19.29	80.90
130-139.....	3	9	15	10	12	49	10.06	90.96
140-149.....	2	1	5	7	11	26	5.34	96.30
150-159.....	..	2	1	4	3	10	2.05	98.35
160-169.....	1	2	3	6	1.23	99.58
170-179.....	..	1	1	0.21	99.79
180-189.....
190-199.....
200-209.....	1	1	0.21	100.00
Total.....	63	70	159	117	78	487		
Mean.....	112.6	116.9	114.0	117.1	126.5	116.8		
Median.....	110.7	116.5	111.8	115.5	124.7	115.2		
Mode.....	106.9	115.7	107.4	112.3	121.1	112.1		

TABLE 4.—*Systolic Blood Pressure of White Prisoners, All Weights*

Pressure in Millimeters	Age, Years						Total
	15-24	25-29	30-39	40-49	50-84	40-84	
80-89.....	7	7	8	6	3	9	31
90-99.....	134	52	78	41	17	58	322
100-109.....	541	260	269	93	30	123	1,193
110-119.....	653	362	362	149	70	219	1,596
120-129.....	516	270	279	112	58	170	1,235
130-139.....	221	126	135	73	48	121	603
140-149.....	74	39	49	47	43	90	252
150-159.....	18	14	11	14	26	40	83
160-169.....	9	4	6	4	11	15	34
170-179.....	...	1	...	3	3	6	7
180-189.....	2	2
190-199.....	3	3	3
200-209.....	1	1	1
210-219.....
220-239.....	1	1	1
240-249.....
250-259.....
260-269.....
270-279.....	1	1	1
Total.....	2,175	1,135	1,197	542	315	857	5,364
Mean.....	117.2	118.0	117.7	120.5	129.2	123.7	118.5
Standard deviation.....	13.1	13.0	13.4	16.1	22.4	19.1	14.5
Probable error of the mean	0.2	0.3	0.3	0.5	0.8	0.4	0.1
Median.....	117.2	116.9	116.7	118.8	126.4	121.1	117.1
Mode.....	114.2	114.7	114.7	115.4	120.8	115.9	114.3
Coefficient of variation....	11.2	11.0	11.4	13.4	17.3	15.4	12.2
Percentage above 140 mm...	4.7	5.2	5.5	12.6	28.2	18.3	7.2

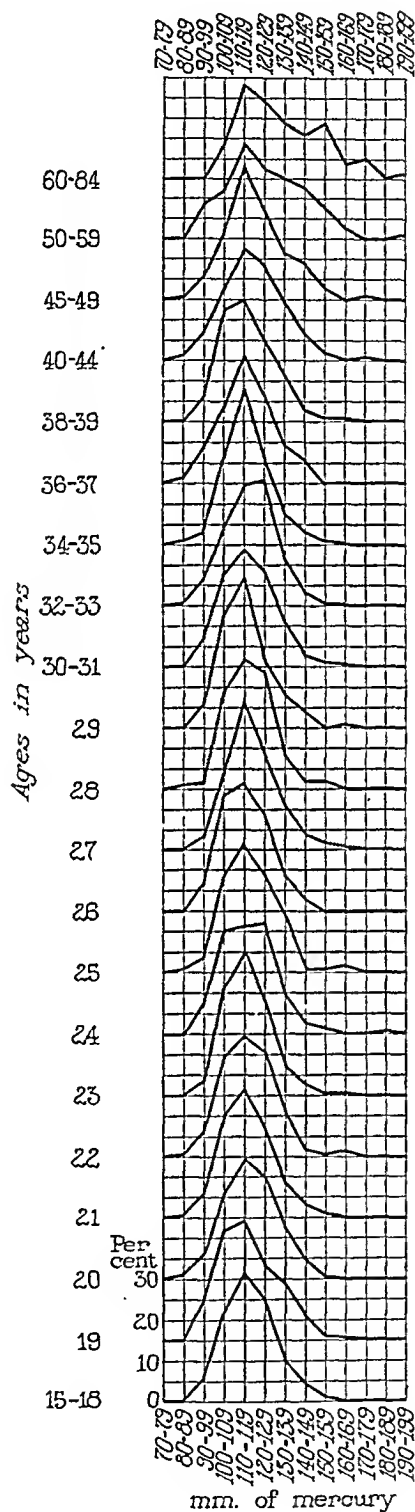


Chart 1.—Percentage distribution polygons showing systolic blood pressure in white prisoners of normal weight and different ages. The ordinates represent percentages; the abscissas represent blood pressure in millimeters of mercury.

to know what normal blood pressure should be for a given patient. The mean or arithmetic average which has been used so commonly in the past is not a reliable index of normal, because it is so markedly affected by the measurements made on persons who are abnormal. In the prisoners studied by us there was so little hypertension, especially among the younger men, that the polygons were fairly symmetrical, and the means year by year were not much larger than the modes. For prisoners of normal weight and middle age the means ranged closely

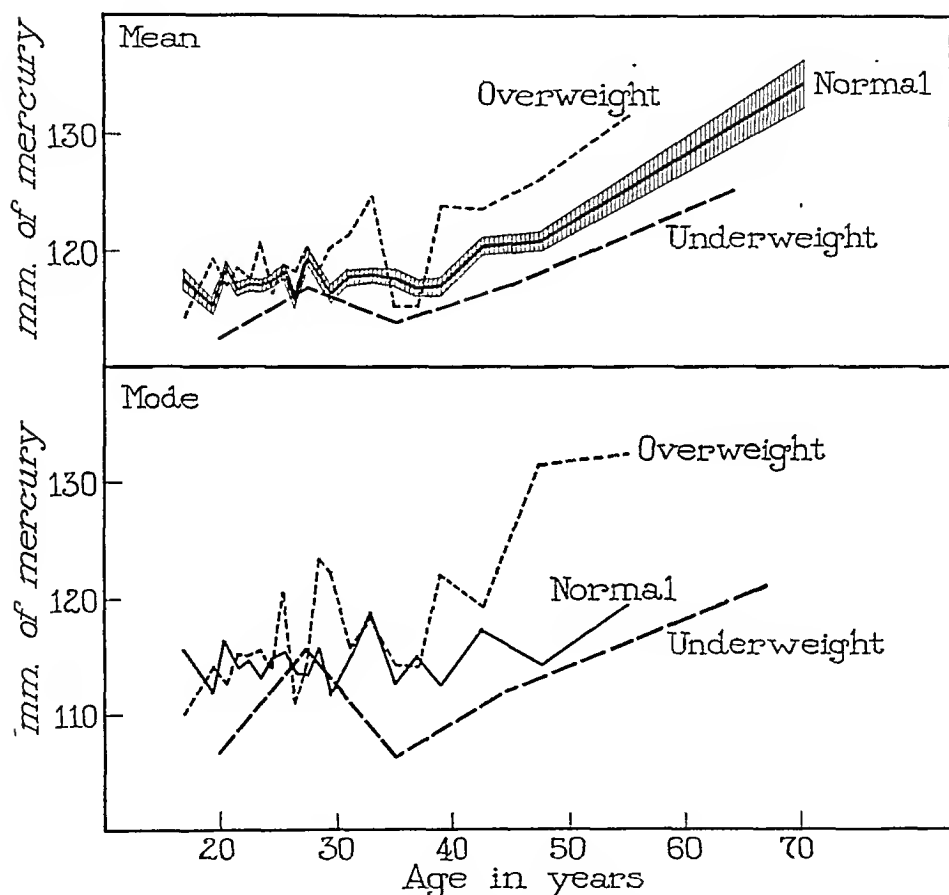


Chart 2.—Mean and modal systolic blood pressures year by year in 5,364 white prisoners. The shaded area on each side of the line which represents the mean shows the range of the probable error of the mean. The lines above and below those representing the means and modes represent mean and modal pressures of prisoners who are 11 per cent or more overweight or 11 per cent or more underweight. The ordinates represent pressures in millimeters of mercury; the abscissas represent ages.

about 117 mm. of mercury. Most of the statisticians who have worked with measurements made during examinations for insurance agree that the means should be about 125 mm.

In chart 1 it can be seen that if the percentage distribution polygons were symmetrical, 140 mm. would represent the upper limit of normal

pressure, and this agrees well with the experience of clinicians and insurance examiners. The lower limit of normal appears to be 90 mm. Taking 140 mm. as the dividing line between normal and pathologic, it appears that 5 per cent of the white prisoners of all weights and ages between 15 and 39 years had hypertension. As will be seen in tables 1 and 4, this percentage was fairly constant in the various age groups, and there were few accessions to the ranks of those with hypertension until after the age of 40 years.

There were few prisoners with pressures higher than 180 mm. At first when we began to study the figures, it seemed to us that there were too few cases of hypertension, and that possibly the examiner might have had a tendency to read low, but later when we came to study the measurements made on prison guards, we saw that this explanation could hardly be correct.

Some readers may be surprised to find that modal blood pressure does not show any tendency to rise until after the age of 45, but as Stocks and Karn⁹ have noted in a recent review of the subject, this absence of a linear correlation between age and blood pressure seems now to be definitely established, and even the averages published by insurance companies demonstrate it (Symonds¹⁰). Still more surprising is the observation recently made by several students of the subject that the mean and modal pressures tend actually to decrease during the third decade of life (Alvarez,³ Burlage⁵). This tendency is shown in chart 6, which represents mean and modal pressure year by year in guards.

The figures of Diehl and Sutherland, when compared with those of Alvarez, show that the younger college entrants are so sensitive and reactive that they respond to excitement with an elevation of blood pressure. With increasing age, they appear to become more phlegmatic, so that after the age of 30 their modal pressure (at the University of California) is almost as low as that of the prisoners.

The fact that in chart 2 the curve representing yearly mean blood pressure begins to rise before that representing modal pressure again brings out the fact that oncoming age causes hypertension to appear in an occasional subject long before it produces a small increase in the pressure of almost everyone in the group. As has already been pointed out, there is a fairly large number of persons in whom hypertension does not develop, no matter how long they live. Of the fifty-eight prisoners aged from 60 to 84 years, and of normal weight, thirty-seven, or 64 per cent, had pressures less than 139 mm. of mercury. Our impression,

9. Stocks, Percy, and Karn, M. N.: *Blood Pressure in Early Life. A Statistical Study*, Cambridge, University Press, 1924, p. 1.

10. Symonds, Brandreth: *The Blood Pressure of Healthy Men and Women*, J. A. M. A. **80**:232 (Jan. 27) 1923.

therefore, is that a pressure of 115 mm. is just as normal and a pressure of 140 mm. just as abnormal in an old man as in a young one.

Chart 2 confirms what is already known (Symonds, Alvarez and Zimmermann,¹¹ Alvarez, McCalla and Zimmermann,¹² and Huber¹³), and that is that fatness and leanness have a definite influence on blood

TABLE 5.—*Systolic Blood Pressure in Negro Prisoners, All Weights*

All Weights					
Pressure in Millimeters	Age, Years				Total
	16-24	25-29	30-39	40-84	
90-99.....	5	2	1	..	8
100-109.....	15	6	8	3	32
110-119.....	25	7	5	2	39
120-129.....	18	7	7	1	33
130-139.....	9	8	6	2	25
140-149.....	5	..	4	2	11
150-159.....	3	3
160-169.....	1	..	1	1	3
170-179.....	1	1
Total.....	81	30	32	12	155
Mean.....	120.3	119.3	123.1	125.8	121.5
Standard deviation.....	15.1	12.6	16.1	22.5	15.8
Probable error of the mean.....	1.1	1.6	1.9	6.5	0.9
Median.....	118.2	120.0	122.9	130.0	119.6
Mode.....	113.7	121.4	122.5	138.4	115.8
Percentage above 140 mm.....	11.1	0.0	15.7	33.3	11.6

Normal Weight					
Pressure in Millimeters	Age, Years				Total
	16-24	25-29	30-39	40-84	
90-99.....	3	2	1	..	6
100-109.....	11	3	6	2	22
110-119.....	12	3	3	2	20
120-129.....	8	5	7	1	21
130-139.....	6	5	3	2	16
140-149.....	1	..	2	1	4
150-159.....	2	2
160-169.....	1	..	1	1	3
170-179.....	1	1
Total.....	44	18	23	10	95
Mean.....	119.3	119.4	122.0	132.0	121.3
Standard deviation.....	14.4	13.4	16.3	22.8	16.9
Probable error of the mean.....	1.4	2.1	2.3	4.9	1.2
Median.....	116.7	122.0	122.1	130.0	119.8
Mode.....	111.4	127.1	122.5	126.0	116.7
Percentage above 140 mm.....	9.1	0.0	13.0	30.0	10.5

11. Alvarez, W. C., and Zimmermann, Arnold: Blood Pressure in Women as Influenced by the Sexual Organs, *Arch. Int. Med.* **37**:597 (May) 1926.

12. Alvarez, W. C.; McCalla, R. L., and Zimmermann, Arnold: Hypertension and Constipation, *Arch. Int. Med.* **38**:158 (Aug.) 1926.

13. Huber, E. G.: Systolic Blood Pressures of Healthy Adults in Relation to Body Weight, *J. A. M. A.* **88**:1554 (May 14) 1927.

pressure. It is not so generally known that leanness and stoutness have little effect on blood pressure until after the age of 37. Alvarez and Zimmermann, who studied 1,182 women (see chart 2 in their article),

TABLE 6.—*Systolic Blood Pressure of Mexican Prisoners, All Weights*

All Weights						
Pressure in Millimeters	Age, Years					Per Cent
	15-24	25-29	30-39	40-68	Total	
80-89.....	1	1	2	0.3
90-99.....	25	10	9	4	48	7.2
100-109.....	67	35	32	9	143	21.6
110-119.....	113	39	41	20	213	31.9
120-129.....	70	40	27	9	146	21.9
130-139.....	32	19	9	8	68	10.2
140-149.....	17	7	5	4	33	4.9
150-159.....	3	3	..	2	8	1.2
160-169.....	1	1	2	0.3
170-179.....
180-189.....	3	3	0.5
Total.....	331	154	124	57	666	100.0
Mean.....	118.0	118.4	116.2	120.8	118.0	.
Standard deviation.....	14.5	14.2	12.7	15.7	14.2	
Probable error of the mean.....	0.5	0.8	0.8	1.4	0.4	
Median.....	116.4	118.0	115.2	117.8	116.6	
Mode.....	113.2	117.2	112.9	111.8	113.8	
Percentage above 140 mm.....	6.9	6.5	4.8	12.3	6.9	
Normal Weight						
Pressure in Millimeters	Age, Years					Per Cent
	15-24	25-29	30-39	40-68	Total	
80-89.....	1	1	0.2
90-99.....	17	6	5	3	31	6.4
100-109.....	45	30	25	6	106	21.8
110-119.....	88	32	30	12	162	33.3
120-129.....	50	26	25	6	107	21.9
130-139.....	25	9	7	4	45	9.2
140-149.....	12	5	5	4	26	5.3
150-159.....	2	3	5	1.0
160-169.....	1	..	1	0.2
170-179.....
180-189.....	3	3	0.6
Total.....	243	111	98	35	487	99.9
Mean.....	118.4	117.6	117.5	119.0	118.1	
Standard deviation.....	14.8	13.5	12.9	14.2	14.1	
Probable error of the mean.....	0.6	0.9	0.9	1.6	0.4	
Median.....	116.6	116.1	116.3	117.1	116.5	
Mode.....	112.7	113.1	113.9	113.3	113.3	
Percentage above 140 mm.....	7.0	7.2	6.1	11.4	7.1	

found that in them fatness began to cause an increase in pressure during the third decade of life while leanness did not lower it much until the fourth decade. When one compares the summaries given in tables 1, 2 and 3, it will be seen that the modal pressure for white prisoners of normal weight was 114.4 mm., that for overweight prisoners was 114.8

mm. and that for underweight prisoners was 112.1. The corresponding means in the three groups were 118.3, 119.9 and 116.8 mm., respectively. These differences are less striking than those that have been found in office patients and in persons examined for insurance.

Racial Differences in Blood Pressure.—Tables 5 and 6, and chart 3 show the distribution and central tendencies of blood pressure in negroes and Mexicans. Unfortunately the groups are a little too small for safe conclusions, but they show that blood pressure in Mexicans does not rise with age, while that in negroes rises more rapidly than in white Americans. The effects of overweight and underweight in the negro and Mexican seem to be about the same as in the white American.

There were forty Chinese of all ages. Twenty-two were normal in weight, and fourteen were underweight. Their modal pressure was 113.6 mm., and their mean pressure was 125.3 ± 1.9 mm.

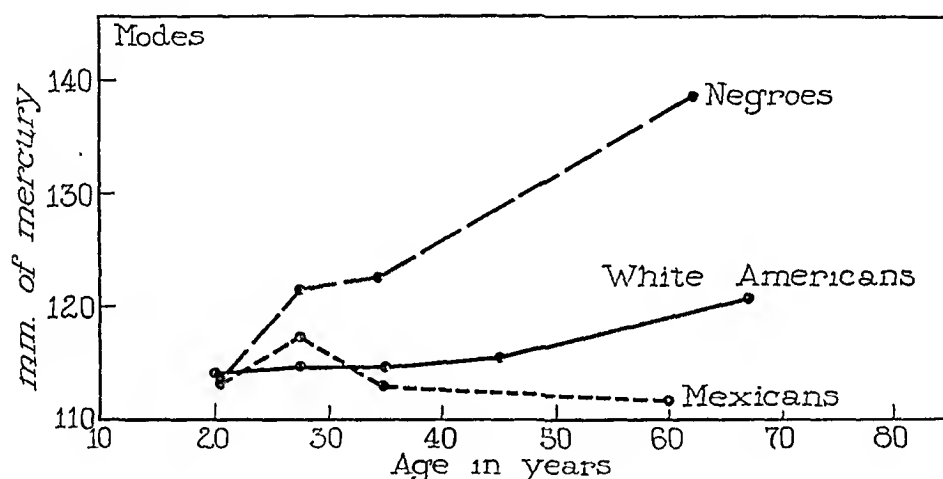


Chart 3.—Modal systolic blood pressure for white American prisoners, for negroes and for Mexicans, of all weights.

Effect of Syphilis.—As pointed out in a recent article (Stanley¹⁴), 9.2 per cent of the prisoners showed a positive Wassermann reaction of the blood. Table 7 and chart 4 suggest that during the first four decades of life syphilis has no effect on systolic blood pressure. After the age of 40 it appears to be beneficial in so far as it helps to maintain a youthful level of pressure.

Effects of the Previous Use of Alcohol and Drugs.—Twenty-one per cent of all the prisoners admitted having used alcohol more or less habitually before their incarceration. Most of them had, for some time before the examination, been deprived of liquor on account of their

14. Stanley, L. L.: Syphilis Among State Prisoners, J. A. M. A. **92**:1238 (April 13) 1929.

TABLE 7.—Systolic Blood Pressure of Syphilitic Prisoners, Normal Weight

Pressure in Millimeters	Age, Years				Total
	16-24	25-29	30-39	40-84	
80-89.....	1	2	3
90-99.....	8	10	6	5	29
100-109.....	33	21	24	18	96
110-119.....	44	30	35	21	130
120-129.....	25	18	22	14	79
130-139.....	12	11	14	4	41
140-149.....	7	2	2	11	22
150-159.....	1	5	6
160-169.....	..	2	1	1	4
Total.....	130	94	105	81	410
Mean.....	116.9	116.8	117.1	120.7	117.6
Standard deviation.....	12.8	13.5	12.9	18.1	14.4
Probable error of the mean.....	0.8	0.9	0.9	1.4	0.5
Median.....	115.5	115.3	116.1	117.4	115.9
Mode.....	112.5	112.7	114.3	110.8	112.5
Percentage above 140 mm.....	6.2	4.3	2.9	21.0	7.8

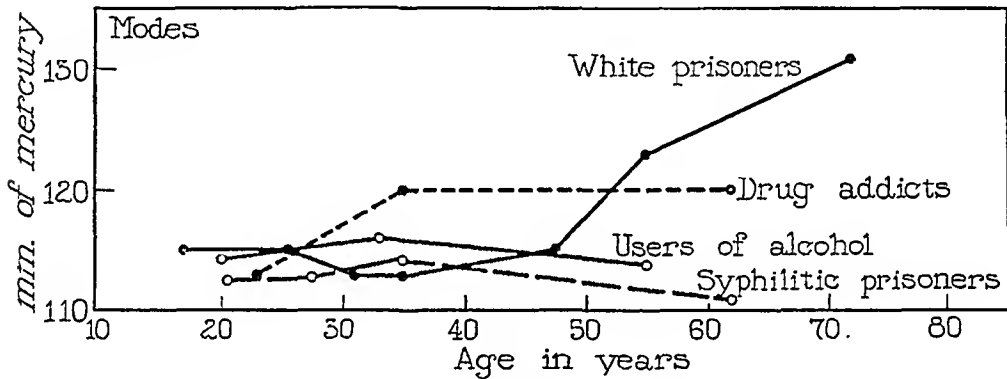


Chart 4.—Modal systolic blood pressure in white healthy prisoners, in drug addicts, in users of alcohol and in prisoners with positive Wassermann reactions, all weighing within 10 per cent of the normal average.

TABLE 8.—Systolic Blood Pressure of Users of Alcohol, Normal Weight

Pressure in Millimeters	Age, Years			Total
	15-25	26-39	40-70	
80-90.....	1	3	..	4
90-99.....	20	7	4	31
100-109.....	87	17	30	134
110-119.....	112	20	58	190
120-129.....	79	16	39	134
130-139.....	40	15	24	79
140-149.....	15	5	16	36
150-159.....	3	2	10	15
160-169.....	...	1	2	3
Total.....	357	86	183	626
Mean.....	117.4	119.0	123.0	119.2
Standard deviation.....	12.7	16.6	14.9	14.2
Probable error of the mean.....	0.5	1.2	0.7	0.4
Median.....	116.3	118.0	119.9	117.6
Mode.....	114.1	116.1	113.7	114.4
Percentage above 140 mm.....	5.0	9.3	15.3	8.6

imprisonment in county jails. The pressures of the 626 who were of normal weight are analyzed in table 8 and chart 4.

All lovers of the cup that cheers will be rejoiced and perhaps encouraged to learn that the mean blood pressure of the users of alcohol was no different from that of the abstainers. Moreover, chart 4 shows that the calculated mode did not tend to rise with age as much as it usually does. Naturally, in order to merit general acceptance, these observations will have to be confirmed on other groups of men, and particularly on groups in which care has been taken to establish for each user of alcohol the amount of the drug consumed, the way in which it was consumed (day by day or in occasional debauches) and the length

TABLE 9.—*Systolic Blood Pressure of Drug Addicts, Normal Weight*

Pressure in Millimeters	Age, Years			Total
	16-29	30-39	40-84	
80-89.....	1	1
90-99.....	1	3	1	5
100-109.....	18	8	3	29
110-119.....	30	13	8	51
120-129.....	17	15	8	40
130-139.....	8	4	4	16
140-149.....	3	3	4	10
150-159.....	1	..	2	3
160-169.....	1	..	1	2
Total.....	80	46	31	157
Mean.....	118.5	118.9	126.6	120.2
Standard deviation.....	13.1	12.4	16.3	14.0
Probable error of the mean.....	1.0	1.2	2.0	0.8
Median.....	116.7	119.2	124.4	118.5
Mode.....	113.0	119.9	119.9	115.2
Percentage above 140 mm.....	6.3	6.5	22.6	9.6

of interval elapsed between the period of the habitual drinking and the taking of the blood pressure. The fact, however, that in this group of prisoners there was no significant difference between the pressures of abstainers and drinkers makes it seem improbable that any will be found in the future.

Two hundred and eighty-four (4.6 per cent) of the 6,225 prisoners admitted having used drugs, but at the time of examination all were, perforce, more or less over the habit. Table 9 and chart 4 suggest that in drug addicts there is a slight increase above normal in the modal pressure during the fourth and fifth decades of life.

Effect of Tobacco.—Six and four-tenths per cent, or 288, of the 4,507 men aged between 15 and 39 years did not use tobacco. In the group aged from 25 to 39 years the percentages of underweight, normal and overweight men were practically the same as in the group of

smokers, but in the group aged from 15 to 24 years the percentage of overweight men was significantly greater than in the corresponding group of smokers.

The mean blood pressure for the nonsmokers was 116.4 ± 0.5 mm. This is 1.2 ± 0.5 mm. less than the mean for 3,931 smokers. As the difference is only twice its probable error, it is hardly significant. Much more significant is the fact that the calculated mode for nonsmokers is low: 110.7 mm. as compared with 114.7 mm. for 4,507 smokers and nonsmokers taken together. The percentage with pressures higher than 140 mm. was 5.9, which is practically the same as that of the 4,507.

TABLE 10.—*Diastolic Blood Pressure of White Prisoners, Normal Weight*

Pressure in Millimeters	Age, Years				Total
	15-24	25-29	30-39	40-84	
20-29.....	3	1	4
30-39.....	7	2	9
40-49.....	40	14	9	6	69
50-59.....	174	73	53	25	325
60-69.....	339	133	151	82	710
70-79.....	348	201	212	107	868
80-89.....	128	79	78	70	355
90-99.....	35	22	31	39	127
100-109.....	3	1	2	6	12
110-119.....	...	1	...	3	4
120-129.....
130-139.....	1	1
Total.....	1,077	531	536	340	2,484
Mean.....	69.0	71.2	72.4	75.9	71.2
Standard deviation.....	11.8	11.5	10.8	13.5	12.0
Probable error of the mean	0.2	0.3	0.3	0.5	0.2
Median.....	69.3	71.9	72.6	75.2	71.4
Mode.....	68.3	63.9	72.9	74.0	70.3

These observations suggest that tobacco raises slightly the pressure of most of its users, but does not produce pathologic hypertension.

To a considerable extent this study confirms that of Johnson,¹⁵ who found no difference in the mean blood pressure of two small groups of smokers and nonsmokers.

The Effect of Warm and Cool Weather.—The mean of the blood pressure readings made on seventy-four prisoners on warm days was $117.8 \text{ mm.} \pm 1 \text{ mm.}$ The mean of another group of 135 men of similar ages, measured on cool days, was $122.7 \pm 0.8 \text{ mm.}$ It would seem obvious from this and other observations made during the past by Oliver¹⁶ and others that if blood pressure readings are to be comparable,

15. Johnson, W. M.: Tobacco Smoking. A Clinical Study, J. A. M. A. **93**: 665 (Aug. 31) 1929.

16. Oliver, George: Studies in Blood Pressure, Physiological and Clinical, ed. 3, London, H. K. Lewis & Company, 1916, pp. 240.

they should always be accompanied by a record of the temperature of the air at the time. It may well be that differences in temperature account for some or all of the differences in mean blood pressure reported by different observers in different places. They may account also for the marked differences in mean pressure observed from year to year in the same place (Alvarez,¹⁷ Diehl and Sutherland, Symonds).

Influence of Type of Crime.—Having in mind the marked influence that excitement and emotion and perhaps temperament have on blood pressure, we were curious to determine whether the readings on murderers would be any different from those made on the other prisoners. There were eighty-one men between the ages of 15 and 39 who had been convicted of first degree murder, and their mean blood pressure was 120.8 ± 1.2 mm. The difference ($+ 3 \pm 1.2$ mm.) between this and the mean for all prisoners of like ages is probably significant. A greater incidence of hypertension in murderers is shown also by the fact that whereas in the whole group of prisoners there were only 7.2 ± 0.2 per cent with pressures over 140 mm., in this special group there were 12.3 ± 2.8 per cent with such pressures.

It is curious that a similar increase in mean blood pressure was not demonstrable either in second degree murderers or in the men who committed assault with a deadly weapon or with intent to kill. This suggests that the mental make-up that permits or causes a man to attempt the killing of his fellows has no permanent effect on the pressure regulating mechanism, and that the slight hypertension observed in many of the first degree, efficient and successful murderers was produced by worry over their trial and punishment.

DIASTOLIC PRESSURE AND PULSE PRESSURE

Chart 5 and table 1 show that the rise in the line representing modal diastolic pressure comes some time before that in the line representing systolic pressure. As a result modal pulse pressure decreases slightly during the years between the ages of 27 and 47. This has been observed by others, and it may help to explain some of the loss of circulatory efficiency that begins to appear during middle life.

The modal diastolic pressure in prisoners aged from 15 to 29 years was about 68 mm.; in those aged from 30 to 84 years it was about 73 mm. Modal pulse pressure decreased gradually from 46.5 mm. at the age of 20 years to 42 mm. at the age of 40 years.

Fatness and leanness each had a slight effect on the diastolic pressure. The mean diastolic pressure of Mexicans, young negroes, users of drugs and prisoners with syphilis appeared to be normal, but the mean for the

17. Alvarez (footnote 3, second reference).

older negroes, aged over 40 years, was 6.6 ± 3 mm. higher than the mean for white Americans of the same age. As one might expect from the prevalence of lesions of the aortic valve in syphilitic persons, the pulse pressure of the older prisoners with a positive Wassermann reaction was a little larger than that of healthy men.

CORRELATIONS BETWEEN BLOOD PRESSURE AND VARIOUS BODY MEASUREMENTS AND BUILDS

It has already been shown in chart 2 that there is a relationship between body weight and systolic blood pressure, particularly during the later years of life. This relationship has been analyzed more minutely in

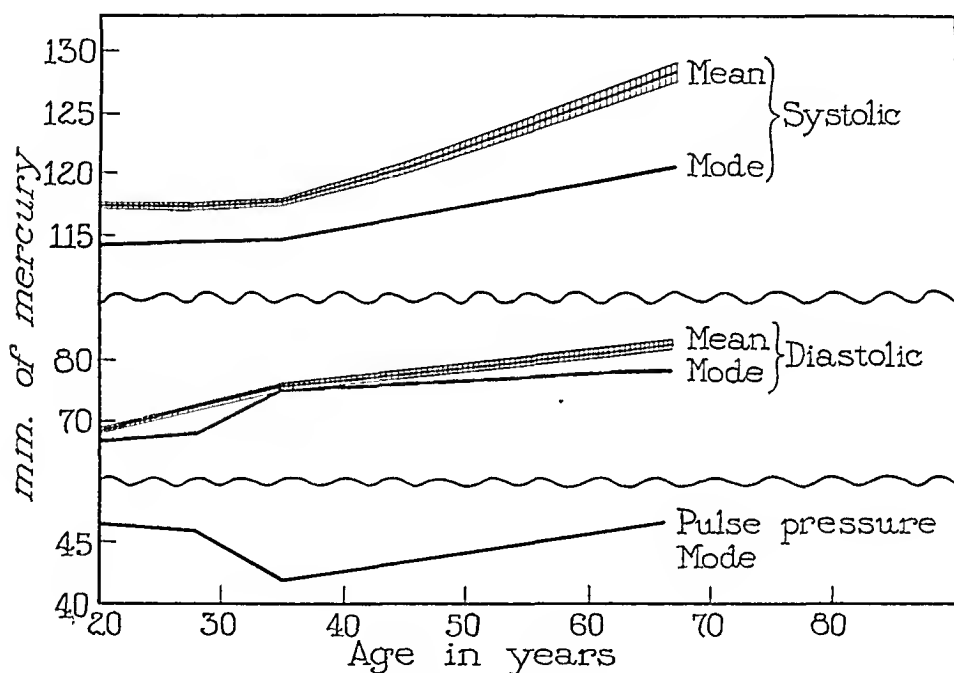


Chart 5.—Mean and modal systolic and diastolic blood pressures in all white prisoners of all weights. The lowest line represents modal pulse pressure. The ordinates represent pressures, and the abscissas represent yearly age groups.

table 11. There it is shown that the coefficient increases from $+0.100 \pm 0.013$ about the age of 20 years to $+0.205 \pm 0.022$ about the age of 35 years, and then decreases to $+0.117 \pm 0.038$ about the age of 60 years.

We have the impression from working with office patients that in them fatness and leanness have more effect on the level of blood pressure than they have in the prisoners, but in the absence of a careful statistical analysis we cannot be positive. The matter is of considerable importance when one is faced with the problem of appraising the significance of a small difference in the mean blood pressure of two groups of men or women. As was shown by Alvarez and Zimmermann, such a differ-

TABLE 11.—*Correlation Tables Showing Relation Between Weight and Systolic Blood Pressure at Different Ages*

Systolic Blood Pressure in Millimeters of Mercury															Total
Weight in Kilograms	Ages, 15-24 Years *														
	80-89	90-99	100- 109	110- 119	120- 129	130- 139	140- 149	150- 159	160- 169	170- 179	180- 189	190- 199	200+		
98+.....	1	...	1	1	3	
94-97.....	1	1	2	
90-93.....	2	1	2	...	1	..	1	7	
86-89.....	8	6	5	3	3	25	
82-85.....	..	3	19	34	16	10	7	1	90	
78-81.....	..	6	24	41	40	20	3	1	135	
74-77.....	..	15	59	63	68	25	9	2	2	243	
70-73.....	1	22	93	115	95	40	14	5	2	387	
66-69.....	2	33	128	142	109	52	14	3	3	..	2	488	
62-65.....	2	17	91	119	89	33	10	2	363	
58-61.....	1	20	80	85	57	23	6	1	273	
54-57.....	1	9	31	26	22	13	2	2	106	
50-53.....	1	8	8	13	8	1	4	1	44	
46-49.....	2	1	3	
Total.....	8	133	545	648	512	221	74	18	8	..	2	2,169	
Ages, 25-29 Years †															
98+.....	2	3	1	1	1	8	
94-97.....	1	...	2	2	1	6	
90-93.....	3	2	3	1	1	10	
86-89.....	4	7	6	4	2	1	24	
82-85.....	..	3	10	16	12	3	4	1	49	
78-81.....	1	5	20	29	12	10	3	1	81	
74-77.....	..	3	20	36	23	25	5	1	118	
70-73.....	1	9	55	72	47	25	7	1	1	218	
66-69.....	1	8	54	77	54	27	10	1	2	1	235	
62-65.....	..	11	50	63	53	4	3	2	1	187	
58-61.....	1	7	29	33	30	15	1	2	118	
54-57.....	1	5	13	19	15	9	2	3	67	
50-53.....	1	...	2	2	2	7	
46-49.....	2	1	1	4	
Total.....	6	51	263	359	268	126	40	14	4	1	1,132	
Ages, 30-39 Years ‡															
98+.....	1	3	2	2	3	..	2	13	
94-97.....	2	2	4	8	
90-93.....	1	1	3	1	2	3	1	12	
86-89.....	8	9	4	3	..	1	25	
82-85.....	..	3	8	15	13	7	2	1	49	
78-81.....	..	4	7	17	19	12	5	1	65	
74-77.....	..	2	17	33	20	11	5	88	
70-73.....	..	7	33	43	48	20	6	1	2	160	
66-69.....	1	12	42	69	47	16	8	1	196	
62-65.....	5	9	40	43	25	14	3	1	140	
58-61.....	1	8	23	24	22	4	3	1	86	
54-57.....	..	4	16	13	4	3	40	
50-53.....	..	4	4	1	..	5	1	15	
46-49.....	..	3	3	6	
Total.....	8	57	207	273	210	100	37	7	4	903	
Ages, 40-49 Years §															
98+.....	1	1	3	2	1	1	9	
94-97.....	..	1	...	4	...	1	6	
90-93.....	1	2	...	2	5	
86-89.....	..	1	1	1	4	3	2	12	
82-85.....	3	3	2	2	1	11	
78-81.....	..	1	7	7	9	3	2	2	..	1	32	
74-77.....	..	1	6	11	7	7	4	1	37	
70-73.....	8	17	14	5	5	1	1	51	
66-69.....	..	5	15	13	13	9	7	62	
62-65.....	..	8	5	14	10	7	3	47	
58-61.....	..	5	9	6	5	3	..	1	29	
54-57.....	2	3	1	1	..	1	1	9	
50-53.....	..	1	1	1	...	1	4	
46-49.....	..	2	1	3	
Total.....	..	25	60	83	68	46	24	7	2	2	317	
Ages, 50-84 Years §															
98+.....	1	...	1	..	1	1	1	5	
94-97.....	2	2	4	
90-93.....	1	1	2	1	1	1	7	
86-89.....	1	3	3	1	1	1	10	
82-85.....	..	4	2	4	1	...	1	1	1	1	..	15	
78-81.....	..	2	2	3	5	3	7	3	1	1	..	1	..	28	
74-77.....	..	1	3	4	6	5	3	2	1	1	26	
70-73.....	..	1	2	5	7	8	6	5	1	1	36	
66-69.....	..	2	9	15	5	8	6	5	1	51	
62-65.....	1	4	6	13	13	7	9	3	56	
58-61.....	..	1	3	9	11	5	3	2	2	1	..	1	1	39	
54-57.....	1	1	...	7	3	4	3	1	20	
50-53.....	1	3	1	1	3	..	2	11	
46-49.....	1	3	1	1	6	
Total.....	4	16	30	69	58	48	43	26	11	3	..	3	3	314	

* $r = +0.100 \pm 0.013$.

† $r = +0.100 \pm 0.020$.

‡ $r = +0.205 \pm 0.022$.

§ $r = +0.179 \pm 0.036$.

§ $r = +0.117 \pm 0.038$.

ence can sometimes be accounted for solely by the fact that the persons in one group are heavier than those in the other.

We expected to find a somewhat better correlation between systolic blood pressure and the percentage of overweight or underweight, but we were disappointed. The coefficients for the younger and for the older men were in each case almost exactly the same as those obtained with the weights alone, unrelated to height.

The degree of overweight or underweight of the prisoners was measured also by means of the fulness index of Rohrer. Since the size of the body varies in three dimensions whereas height varies in only one, it has been thought best, when comparing height with weight, either to cube the one or else to extract the cube root of the other. Actually, in Rohrer's method, one divides the weight in kilograms by the cube of the height in centimeters.

Unfortunately, this index is affected not only by the amount of fat in the body but also by the relative length of the trunk and the legs. For this reason it is a better criterion of normal body weight in subjects of normal stature than in those who are short or tall. But even with this handicap the index correlated well with the figure expressing percentage of overweight or underweight. The coefficient was $+0.897 \pm 0.005$ for ages from 16 to 20, and $+0.923 \pm 0.005$ for ages from 30 to 33. The coefficient representing correlation between systolic blood pressure and the fulness index was, for ages from 20 to 39, $+0.104 \pm 0.012$ and for ages from 40 to 84, $+0.177 \pm 0.028$. Again, these figures are practically the same as those obtained with the weight uncorrected for height.

We could not demonstrate any correlation between blood pressure and height, or, during the early years of adult life, any correlation between blood pressure and surface area. During the later years of life, there appears to be a small positive correlation between systolic pressure and surface area. The coefficient was, for the ages from 20 to 25, $+0.072 \pm 0.020$ and for ages from 40 to 84, $+0.126 \pm 0.029$.

It has often been stated that hypertension occurs more often in the stocky, short-necked type of man than in the tall, thin, long-chested type, but so far as we know little work has been done to prove the point. Before we could make correlation tables we had to have some index of stockiness or ranginess, some figure to express numerically the relation between volume of trunk and volume or length of the lower limbs. After some investigation we chose the "pyknic index" which according to Wertheimer and Hesketh¹⁸ is the most satisfactory of the various

18. Wertheimer, F. I., and Hesketh, F. E.: A Minimum Scheme for the Study of the Morphologic Constitution in Psychiatry, *Arch. Neurol. & Psychiat.* 17:93 (Jan.) 1927.

indexes devised by anthropologists. It is obtained by substituting in the following formula:

$$\frac{\text{Leg length} \times 1,000}{\text{Transverse chest diameter} \times \text{sagittal chest diameter} \times \text{trunk height (to supra-sternal notch)}} \times 100$$

Using records of prisoners aged from 17 to 39 years, we could find no correlation between systolic pressure, and the "pyknic index." The coefficient was -0.089 ± 0.054 . Apparently, then, there is little justi-

TABLE 12.—Systolic Blood Pressure of 442 Guards, All Weights

Pressure in Millimeters	Age, Years				Total
	16-24	25-29	30-39	40-66	
90-99.....	1	..	2	3	6
100-109.....	5	4	20	8	37
110-119.....	4	12	28	30	74
120-129.....	3	13	46	40	102
130-139.....	4	12	29	40	85
140-149.....	4	2	19	33	58
150-159.....	2	1	5	28	36
160-169.....	..	1	4	12	17
170-179.....	12	12
180-189.....	1	6	7
190-199.....	1	5	6
200-209.....	1	1
210-219.....
220-229.....
230-239.....	1	1
Total.....	24	45	154	219	442
Mean.....	127.9	127.2	127.0	140.2	133.5
Standard deviation.....	20.9	12.2	15.8	22.9	20.8
Probable error of the mean....	2.9	1.2	0.9	1.0	0.7
Median.....	126.7	125.0	125.9	137.1	130.2
Mode.....	124.2	120.6	123.6	131.0	123.8
Percentage above 140 mm.....	29.2	8.9	18.8	44.8	31.3

fication at present for the belief that there is a relation between body build and blood pressure.

Only one correlation coefficient was calculated for diastolic pressures and that was for diastolic pressure and the fulness index. For prisoners aged from 20 to 25 years there was no correlation.

STUDIES ON GUARDS

Table 12 and chart 6 summarize the measurements made on 442 guards. We were surprised to find their pressures so much higher than those of the prisoners. Some of the difference is probably due to the fact that the guards are considerably heavier than the prisoners. Unfortunately measurements of height and weight were not made when the guards were examined, and hence we cannot compute how much of the observed difference in pressure is due to the difference in weight.

We have already referred to the fact that the men whom we designate here as guards were examined at a time when they were applicants for the position, and when they were much concerned for fear that something would be found to cause their rejection. The prisoners naturally had no such worries and hence could look on the examination with only a mild interest. In trying to account for the large numbers of guards with hypertension, it must be remembered also that some of them would probably never have applied for a lazy man's job if they had not been somewhat unfit and doubtful of their ability to lead a normally strenuous and successful life.

It is remarkable that 29 per cent of the guards aged from 16 to 24 years and 44.8 per cent of those aged from 40 to 66 years showed pressures higher than 140 mm. of mercury. As will be remembered, the corresponding figures for the prisoners were much smaller.

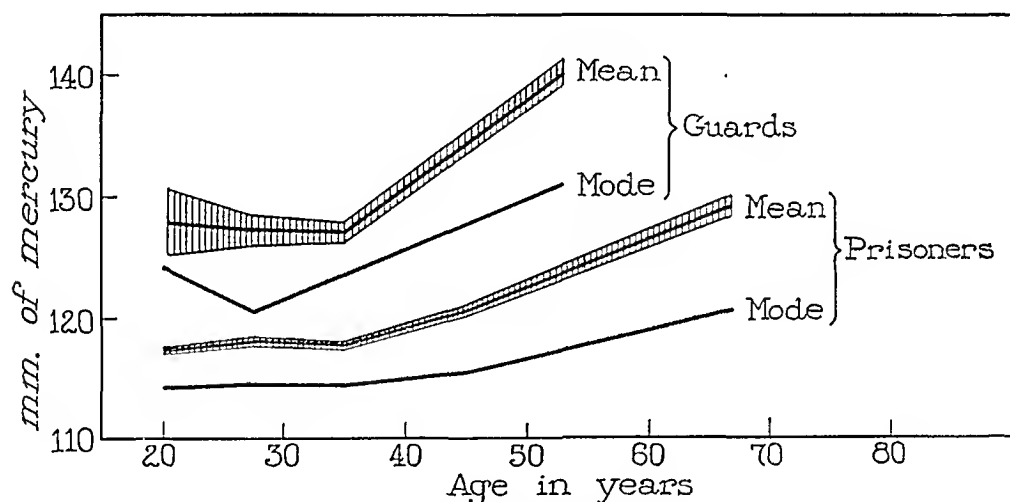


Chart 6.—Mean and modal systolic blood pressure of white prisoners and guards, of all weights. The shaded area represents the limits of probable error of the mean.

COMMENT

Again it has been demonstrated that the level of pressure in most persons does not rise even in old age. Many of those who are found to have hypertension during the fifth decade of life probably had it already by the end of the second. That this is true is suggested by the fact, already commented on, that the percentage of men with pressure levels higher than 140 mm. remains practically the same from the age of 15 until the age of 40 years. If during this time there were many accessions to the ranks of those with hypertension, one would expect this percentage to increase. It may be, however, that the mortality in this group is such that the losses balance the accessions.

We have been impressed by the fact that the level of blood pressure seems to be little affected by such factors as dissipation, the use of

alcohol and drugs, or even by so chronic an infection as syphilis. It appears to be affected largely by heredity, and it certainly is affected by excitement, nervous strain, the day's work, the amount of fat in the body and the temperature of the air.

SUMMARY

There is need for more knowledge about biologic variations in blood pressure in groups of men and women chosen at random from the nation.

In the prisoners studied, modal blood pressure varies but little from youth to old age. Mean pressure does not increase until after the age of 40 years. In the years from 20 to 40 the percentage of men with pressures higher than 140 mm. of mercury remains almost constant. This suggests that all those who have hypertension at the age of 40 had it at the age of 20. The percentage distribution polygons show that the lower limit of normal pressure is about 90 mm., whereas the upper limit is about 140 mm.

The modal or most typical pressure is the one which should be studied when one wants to know what normal blood pressure is. In the prisoners it is about 115 mm. of mercury. This is lower than the figure usually found for men out in the world. The reason may be that the prisoners are not fatigued and worried by the struggle to make a living; to a certain extent their pressures are basal.

It appears from this study that a pressure of 115 mm. is just as normal and a pressure of 140 mm. is just as abnormal in an old man as in a young one.

After the age of 35 years, fatness tends to increase blood pressure and thinness tends to decrease it.

The older Mexican prisoners rarely show the increase in blood pressure which is seen so commonly in natives and residents of the United States. In the older negroes, however, this increase is more than usually striking. It is absent in syphilitic prisoners.

Judging from this study, the use of alcohol has no effect on blood pressure. Drug addicts appear to have slightly increased blood pressures during the years of middle life. The use of tobacco by young men appears to raise the modal pressure about 4 mm. It does not appear to produce pathologic hypertension. Cool weather slightly raises the level of mean blood pressure.

The men convicted of murder in the first degree have a mean pressure 3 ± 1.2 mm. higher than that of other prisoners of like ages. Strange to say, those who only attempted murder or who were convicted of second degree murder have normal pressures.

Modal diastolic pressure is 68.5 mm. in the younger men, and 73 mm. in the older men. Diastolic pressure tends to rise several years earlier than systolic pressure. As a result, pulse pressure decreases during the fourth decade of life. Fatness and leanness have a slight effect on diastolic pressure.

In middle-aged men there is a slight correlation between systolic blood pressure and weight, and also between systolic pressure and surface area. There is no correlation with height or with the degree of stockiness or ranginess. Contrary, then, to the general impression, thick-set, stocky men are apparently no more likely to develop hypertension than are their tall, thin, asthenic-looking brethren.

The prison guards have pressures considerably higher than those of the prisoners. This may be due partly to overweight and partly to the fact that at the time the measurements were taken the guards were applying for a position, and many were anxious for fear something would be found to cause their rejection.

THE METABOLISM OF OBESITY

VII. THE AFTER-EFFECT OF MUSCULAR EXERCISE ON THE PRODUCTION OF BASAL HEAT*

CHI CHE WANG, PH.D.

SOLOMON STROUSE, M.D.

AND

EDITH SMITH, B.S.

CHICAGO

It has been a question in the minds of many clinicians and investigators whether the thirty minute rest period commonly used before basal metabolic tests served as sufficient time for the body to come to basal conditions especially in the case of patients who come from a distance. Benedict and Crafts¹ demonstrated that after a thirty minute rest the energy metabolism of normal women was only slightly increased following muscular exercise consisting of the usual morning routine as compared with the test made after a night's rest in bed. The question arose whether these observations would be applicable to obese and underweight subjects, and further whether subjects who had more vigorous exercise would require a longer period of rest. The present investigation was therefore undertaken.

EXPERIMENTAL WORK

A total of forty-one experiments consisting of four tests each were conducted on thirty-five women, thirteen of whom were obese, fifteen normal and seven underweight. With the exception of two obese subjects, who were 55 and 56 years old, the group ranged from 18 to 31 years of age. The variation for the normal group was from 19 to 38 years, while that for the underweight group was from 20 to 38 years. The percentage deviations from the standard weight² ranged from +85.1 to +13.3 with an average of +49.7 in the obese group. The corresponding values in the normal and underweight groups, respectively, were from +8 to -7.9 with an average of -1.6, and from -15.1 to -26.4 with an average of -20.7 per cent.

* Submitted for publication, Nov. 1, 1929.

* From the Medical Clinic, the Gusta Morris Rothschild Fund and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Benedict, Francis G., and Crafts, Elizabeth E.: Is Prolonged Bed Rest a Prerequisite for the Measurement of Metabolism? *Am. J. Physiol.* **74**:369, 1925.

2. Association of Life Insurance Medical Directors and Actuarial Society of America, *Medico Actuarial Mortality Investigation*, 1912.

The production of heat was measured by the Tissot gasometer in connection with a Haldane gas analysis apparatus. The bicycle ergometer, which was described in one of our previous papers,³ was employed for the measurement of muscular exercise. All the experiments were performed under a postabsorptive condition. Following a thirty minute rest period the basal test of ten minutes was taken; this was followed by another test made while the subject was riding the ergometer at a speed of about 120 revolutions per minute and with a load of about six pounds (2.7 Kg.). The period of exercise varied in length from three and five-tenths to six and two-tenths minutes depending on the subject's ability. The third and fourth tests were made fifteen and thirty minutes after the exercise.

COMMENT

A higher production of heat than the basal value was found in thirty of forty-one experiments made fifteen minutes after the exercise. The values are given in tables 1, 2 and 3. However, only thirteen were 10 per cent or more above the basal. Six of the thirteen were from the obese, two from the normal and five from the underweight group. The average differences from the basal value in the three groups were +6.5, +3.1 and +6.8 per cent, respectively. The production of heat for all the subjects thirty minutes after exercising varied from +10.5 to -10.3 per cent from their basal value. Twenty-seven subjects showed a lower, eight a higher and six the same value as that fifteen minutes after exercising. No great difference from muscular exercise was observed in the recovery period in the three groups. The average variation from the basal value thirty minutes after the exercise was +0.9, +0.8 and -0.1 per cent for the obese, normal and underweight subjects, respectively.

With the lowering of the production of heat there was a lowering of the respiratory quotient in all three groups. Thus the average respiratory quotients for the obese group were 0.759 for the basal value, 0.889 for the exercising, 0.822 fifteen minutes after the exercise and 0.748 thirty minutes after the exercise. The corresponding values for the normal group were 0.755, 0.921, 0.775 and 0.728, while those for the underweight group were 0.767, 0.971, 0.837 and 0.749. This variation in the respiratory quotient following exercise and subsequent rest periods is in agreement with that reported by Benedict and Cathcart⁴ who found

3. Wang, Chi Che; Strouse, Solomon; and Morton, Zelma Owen: Studies on the Metabolism of Obesity: V. Mechanical Efficiency, *Arch. Int. Med.* **45**:727 (May) 1930.

4. Benedict, Francis G.; and Cathcart, Edward P.: Muscular Work. A Metabolic Study with Special Reference to the Efficiency of the Human Body as a Machine, Carnegie Institution of Washington, 1913, Bulletin 187.

TABLE 1.—Heat Production Before and After Muscular Exercise in Obese Subjects

Subject	Sex	Age	Height Kg.	Weight		Basal Test			Exercising With Brake			Work Done per Hour, Calories	15 Minutes After Exercise			30 Minutes After Exercise		
				Per Cent Difference from Normal	Respir- atory Quo- tient	Calories per Hour Found	Benedict- Harris Difference, per Cent	Respir- atory Quo- tient	Total Calories per Hour	Per Cent Difference from Basal	Respir- atory Quo- tient		Total Calories per Hour	Per Cent Difference from Basal	Respir- atory Quo- tient	Total Calories per Hour	Per Cent Difference from Basal	
H. B.	F	18	175.3	118.6	+85.1	0.765	84	— 4.6	0.836	379	+351.3	55	0.825	90	+ 7.1	0.739	82	— 2.4
H. B.	F	18	175.5	118.5	+84.3	0.765	82	— 2.7	0.864	365	+343.3	51	0.914	93	+13.4	0.789	89	+ 8.5
S. L.	F	32	145.0	92.6	+77.2	0.812	72	+ 3.8	0.974	417	+481.6	79	0.876	76	+ 5.6	0.746	70	— 2.8
E. H.	F	30	163.4	111.1	+73.4	0.817	73	— 7.8	0.908	343	+373.3	59	0.829	74	+ 1.4	0.777	72	— 1.4
E. H.	F	31	163.1	110.2	+72.0	0.691	77	— 1.4	0.855	326	+323.0	53	0.810	87	+13.0	0.691	79	+ 2.6
E. H.	F	31	167.9	105.4	+65.6	0.715	70	— 7.9	0.810	321	+357.2	55	0.886	80	+14.3	0.721	72	+ 2.9
L. K.	F	29	151.0	87.3	+64.1	0.795	63	— 7.7	0.940	351	+457.7	59	0.892	74	+17.5	0.744	62	— 1.6
M. C.	F	19	161.5	85.9	+54.9	0.685	74	+ 5.8	0.827	320	+330.2	57	0.771	79	+ 6.8	0.694	72	— 2.7
E. F.	F	23	166.1	85.7	+43.9	0.765	61	—13.2	0.864	322	+431.3	52	0.790	65	+ 6.6	0.755	66	+ 8.2
K. W.	F	19	160.8	78.5	+42.8	0.718	62	— 7.6	0.907	308	+395.1	47	0.706	62	+ 0.0	0.714	60	— 3.2
E. F.	F	19	154.9	71.4	+37.7	0.762	53	— 9.4	0.906	295	+408.0	48	0.721	52	—10.3	0.707	52	—10.3
E. R.	F	33	151.4	69.2	+23.7	0.756	53	—10.9	0.912	309	+433.0	56	0.806	60	+13.2	0.787	57	+ 7.5
B. C. H.	F	55	156.2	77.0	+22.3	0.799	52	—12.6	0.907	256	+395.0	57	0.851	58	+11.5	0.807	57	+ 9.6
L. R.	F	56	154.4	72.0	+17.3	0.777	53	+ 2.1	0.902	299	+414.6	49	0.953	63	+ 8.6	0.757	55	— 5.2
T. A.	F	21	160.0	65.3	+16.8	0.762	57	— 7.0	0.842	267	+365.3	54	0.778	58	+ 1.8	0.793	63	+10.5
B. R.	F	20	156.7	61.3	+13.3	0.780	62	+ 3.1	0.966	286	+362.9	50	0.750	58	— 6.5	0.753	58	— 6.5
Average.....		28	160.8	88.1	+49.7	0.759	66	— 4.8	0.889	322	+392.0	55	0.822	70	+ 6.5	0.749	66	+ 0.9

TABLE 2.—Heat Production Before and After Muscular Exercise in Normal Subjects

Subject	Sex	Age	Height	Weight		Basal Test			Exercising With Brake			Work Done Hour, Calories	15 Minutes After Exercise			30 Minutes After Exercise		
				Kg.	Per Cent Difference from Normal	Respiratory Quo- tient	Calories per Hour Found	Benedict- Harris Difference, per Cent	Respiratory Quo- tient	Total Calories per Hour	Per Cent Difference from Basal		Respiratory Quo- tient	Total Calories per Hour	Per Cent Difference from Basal	Respiratory Quo- tient	Total Calories per Hour	Per Cent Difference from Basal
E. B.	F	24	161.8	61.4	+8.0	0.758	57	— 3.8	0.993	302	+427.3	53	0.746	57	± 0.0	0.749	59	+3.5
D. T.	F	20	153.4	56.2	+6.6	0.778	53	— 8.6	0.953	263	+399.7	51	0.765	55	+ 3.8	0.749	55	+3.8
R. B.	F	26	158.8	57.6	+4.4	0.725	54	— 6.4	0.893	292	+332.0	59	0.773	48	—11.1	0.717	50	—7.4
N. H.	F	21	161.0	58.8	+4.2	0.743	50	—15.8	0.909	268	+440.0	51	0.764	52	+ 4.0	0.732	54	+8.0
E. M.	F	19	163.3	57.3	+1.6	0.776	58	— 1.7	0.918	261	+349.4	55	0.765	56	— 3.4	0.753	55	—5.2
I. G. S.	F	24	152.4	52.4	+0.2	0.760	50	— 8.2	0.862	223	+342.3	60	0.761	53	+ 6.0	0.748	52	+4.0
E. A. G.	F	27	164.6	59.4	—0.5	0.735	60	+ 2.3	0.855	237	+297.7	56	0.781	62	+ 1.7	0.621	60	+0.0
A. G.	F	19	151.4	50.3	—1.1	0.720	47	—14.3	0.786	222	+360.0	55	0.771	47	± 0.0	0.787	50	+6.4
M. W.	F	21	154.7	52.2	—1.9	0.767	55	— 2.5	0.807	285	+421.7	56	0.786	54	+ 1.8	0.736	58	+5.5
E. G.	F	19	160.7	53.6	—2.5	0.835	54	— 6.8	0.975	293	+448.5	55	0.786	54	± 0.0	0.802	54	+1.9
P. D.	F	38	153.4	55.0	—3.2	0.731	53	— 1.7	0.978	328	+322.7	57	0.774	60	+13.2	0.690	54	—9.4
V. A.	F	27	151.1	49.9	—6.2	0.789	53	— 4.7	0.964	266	+420.8	54	0.760	57	+ 7.5	0.672	48	—4.2
E. S.	F	19	154.9	48.3	—6.8	0.775	48	—11.6	0.972	268	+452.5	56	0.820	50	+ 4.2	0.747	50	+4.2
V. A.	F	27	152.4	50.0	—6.8	0.765	46	—14.8	1.000	267	+483.1	59	0.822	52	+13.0	0.649	45	—2.2
F. M.	F	19	160.5	51.2	—6.9	0.717	54	— 4.0	0.918	288	+433.8	55	0.781	57	+ 5.6	0.759	55	+1.9
F. M.	F	19	160.5	50.7	—7.8	0.717	54	— 4.0	0.908	234	+427.1	57	0.761	58	+ 7.4	0.751	54	±0.0
J. W.	F	35	172.1	63.2	—7.9	0.748	62	+ 5.7	0.909	264	+323.1	46	0.797	61	— 1.6	0.711	61	—1.6
Average....		24	158.0	54.4	—1.6	0.755	53	— 5.9	0.921	268	+404.7	55	0.775	54	+ 3.1	0.738	54	+0.8

TABLE 3.—*Heat Production Before and After Muscular Exercise in Underweight Subjects*

Subject	Sex	Age	Height	Kg.	Weight		Basal Test		Exercising With Brake			Work Done per Hour, Calories	15 Minutes After Exercise			30 Minutes After Exercise			
					Per Cent Difference from Normal	Respiratory Quotient	Calories per Hour Found	Benedict-Harris Difference, per Cent	Respiratory Quotient	Total Calories per Hour	Per Cent from Basal		Respiratory Quotient	Total Calories per Hour	Per Cent from Basal	Respiratory Quotient	Total Calories per Hour	Per Cent from Basal	
O. S.	F	21	162.3	48.6	-15.1	0.774	49	-10.4	0.979	264	+435.8	53	53	0.765	54	+10.2	0.752	52	+0.1
O. D.	F	25	157.7	46.6	-16.0	0.729	48	-10.3	0.865	230	+382.9	59	59	0.829	53	+10.4	0.600	44	-8.3
E. K.	F	38	160.0	48.8	-18.7	0.837	53	+2.8	0.932	220	+313.6	59	59	0.903	59	+11.3	0.765	51	-8.8
O. D.	F	25	158.2	45.4	-18.9	0.739	50	-5.2	0.980	256	+413.7	54	54	0.727	48	-4.0	0.772	49	-2.0
M. O.	F	25	159.0	44.1	-21.8	0.766	49	-6.5	1.010	273	+458.7	63	63	0.827	55	+12.2	0.713	50	+2.0
M. B.	F	23	167.1	45.8	-23.7	0.809	57	+5.2	0.975	269	+374.1	56	56	0.916	64	+12.3	0.727	59	+3.5
V. S.	F	20	156.2	40.0	-25.4	0.749	54	+5.8	0.949	250	+360.4	49	49	0.740	51	± 0.0	0.753	52	-3.7
V. P.	F	25	159.0	41.5	-26.4	0.732	58	+9.4	0.987	281	+402.4	59	59	0.986	59	+1.7	0.904	55	-5.2
Average....		25	159.9	45.1	-20.7	0.767	52	-1.2	0.971	255	+392.7	57	57	0.837	56	+6.8	0.749	52	-0.1

in most cases a high respiratory quotient during exercise and a decrease during the subsequent rest period.

Based on the observations in all three groups, a thirty minute period gave a satisfactory rest before a basal metabolic test following the muscular exercise. These results are in accordance with those found by Benedict and Crafts¹ in their study of normal subjects.

SUMMARY

A total of forty-one experiments consisting of four tests each were conducted on thirty-five women, thirteen of whom were obese, fifteen normal and seven underweight.

The average values for the production of heat fifteen minutes after muscular exercise were $+6.5$, $+3.1$ and $+6.8$ per cent above the basal value for the obese, normal and underweight subjects, respectively.

The corresponding values thirty minutes after the exercise were $+0.9$ and $+0.8$ and -0.1 per cent.

The lowered production of heat after exercise was accompanied by a lowered respiratory quotient.

Based on our observations, a thirty minute rest served as an adequate resting period for the measurement of the production of basal heat.

THE METABOLISM OF NORMAL AND LEUKEMIC LEUKOCYTES *

EUGENE C. GLOVER, M.D.

GENEVA A. DALAND, S.B.

AND

HENRY L. SCHMITZ, M.D.

BOSTON

It has been recognized for some time that leukocytes have a remarkable power of transforming dextrose into lactic acid¹ and that they consume a considerable amount of oxygen.² In normal blood, the leukocytes are present in such small numbers that their oxygen consumption is difficult to measure. The erythrocytes, enormously outnumbering them, also show a small but definite oxygen consumption.³ The sugar consumption of normal blood is due in a large part to the erythrocytes.⁴ When the number of white blood cells is increased, as in leukemia, the blood shows a greatly augmented consumption of oxygen,⁵ and a rapid consumption of sugar,⁶ due to the metabolism of the white blood cells. The metabolism of the blood platelets is comparatively insignificant because of their small size.

* Submitted for publication, Nov. 22, 1929.

* Assistance has been given to us by Dr. George R. Minot.

* From the Thorndike Memorial Laboratory of the Boston City Hospital and the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.

* A part of this work was done under a Bullard Fellowship of the Harvard Medical School (George Cheyne Shattuck Memorial Fellowship), and a part under a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

1. Levene, P. A., and Meyer, G. M.: On the Action of Leucocytes on Glucose, *J. Biol. Chem.* **12**:265, 1912.

2. Grafe, E.: Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, *Deutsches Arch. f. klin. Med.* **102**:406, 1911.

3. Harrop, G. A., Jr.: The Oxygen Consumption of Human Erythrocytes, *Arch. Int. Med.* **23**:745 (June) 1919. Kawashima, Y.: Ueber die glykolytische Kraft des Blutes: III. Mitteilung. Untersuchungen über die Beziehung zwischen der glykolytische Kraft und der O₂-Zehrung der Erythrozyten, *J. Biochem.* **4**: 411, 1925.

4. Maclean, H., and Weir, H. B.: The Part Played by the Different Blood Elements in Glycolysis, *Biochem. J.* **9**:412, 1915.

5. Daland, G. A., and Isaacs, R.: Cell Respiration Studies: II. A Comparative Study of the Oxygen Consumption of Blood from Normal Individuals and Patients with Increased Leucocyte Counts (Sepsis; Chronic Myelogenous Leukemia), *J. Exper. Med.* **46**:53, 1927. Grafe (footnote 2).

6. Bürger, M.: Untersuchungen über Hämoglykolyse, *Ztschr. f. d. ges. exper. Med.* **31**:1, 1923. Maclean and Weir (footnote 4).

Warburg⁷ and his associates have shown that it is possible to demonstrate fundamental differences of metabolism between cancer, embryonic and normal adult tissues by a study of their consumption of oxygen and of sugar under aerobic and anaerobic conditions. The white blood cells have been studied in this manner, and have been shown to have a metabolism different from that of almost all other normal tissues. Exudate leukocytes have been shown to resemble cancer in their metabolism,⁸ while the metabolism of leukocytes from the blood and bone-marrow simulates closely that of embryonic tissues.⁹ These investigations have all been confined to the leukocytes of lower animals and birds.

The metabolism of human leukocytes has also been studied, by somewhat different methods, however. In leukemic blood, the mature and immature leukocytes differ markedly as regards consumption of both oxygen and sugar. Daland and Isaacs¹⁰ have shown that, other things being equal, the oxygen consumption of leukemic blood tends to be greater, the greater the percentage of mature leukocytes. On the other hand, Schmitz and Glover¹¹ demonstrated that the consumption of sugar tends to be less, the more mature the cells. Earlier work by Falcon-Lesses¹² was likewise suggestive of this fact. A somewhat similar observation has been reported by Tamiya and by Hawkins,¹³ who found that the anaerobic sugar consumption of liver tissue (of chickens) decreases as the animal grows from the embryonic stage to maturity.

A more extensive study of the metabolism of normal and leukemic leukocytes has been undertaken and forms the subject of this paper. For the determination of sugar consumption, or glycolysis, suspensions of leukocytes have been used, thus eliminating the rather large and variable factor of sugar consumption by the erythrocytes and making it possible to calculate the sugar consumption of a given number or volume of leukocytes. This cannot be done in experiments with whole blood.

7. Warburg, O.: Ueber den Stoffwechsel der Tumoren, Berlin, Julius Springer, 1926.

8. Bakker, A.: Einige Uebereinstimmungen im Stoffwechsel der Carcinomzellen und Exsudatleukocyten, *Klin. Wchnschr.* **6**:252, 1927. Fleischmann, W., and Kubowitz, F.: Ueber den Stoffwechsel der Leucocyten, *Biochem. Ztschr.* **181**:395, 1927.

9. Fujita, A.: Ueber den Stoffwechsel der weissen Blutzellen, *Klin. Wchnschr.* **7**:897, 1928. Fleischmann and Kubowitz (footnote 8, second reference).

10. Daland and Isaacs (footnote 5, first reference).

11. Schmitz, H. L., and Glover, E. C.: Glycolysis in Leukemic Blood, *J. Biol. Chem.* **74**:761, 1927.

12. Falcon-Lesses, M.: Glycolysis in Normal and Leukemic Blood, *Arch. Int. Med.* **39**:412 (March) 1927.

13. Tamiya, C.: Ueber den Stoffwechsel der Leber in verschiedenen Stadien ihrer Entwicklung, *Biochem. Ztschr.* **189**:175, 1927. Hawkins, J. A.: Metabolism of Liver Tissue from Rats of Different Ages, *J. General Physiol.* **11**:645, 1928.

Oxygen consumption, on the other hand, has been most successfully determined in whole blood, the oxygen consumption of the red blood cells being so small in comparison to that of the leukocytes that it can be neglected. It has also been determined in suspensions of white blood cells.

The purpose of this investigation was to answer two questions: 1. Does the metabolism of white blood cells, measured by improved quantitative methods, bear a definite relationship to the degree of maturity of the cells? 2. Does the metabolism of leukemic white blood cells differ from that of normal white blood cells as the metabolism of cancer tissue differs from that of normal tissue, thus giving evidence that leukemia is an essentially malignant disease?

* MATERIAL AND METHODS

For the study of the oxygen consumption of the white blood cells, whole blood specimens from fourteen patients with myelogenous leukemia and eight patients with lymphatic leukemia have been employed. Suspensions of leukocytes from eighteen patients with myelogenous leukemia, ten patients with lymphatic leukemia, six patients with leukocytosis from various causes and seven normal persons have also been studied. In many cases a number of experiments were performed on successive blood specimens taken from the same patient at intervals of days or months.

For the study of sugar consumption, or glycolysis, suspensions of leukocytes in plasma have been prepared from the blood specimens of sixteen patients with myelogenous leukemia, fifteen patients with lymphatic leukemia and eleven persons with normal blood. Four patients having leukemia of an extremely acute type which could not be definitely classified were also studied. In one series of experiments the sugar consumption was determined during incubation at 37 C. without shaking. In a second series, the suspensions were gently shaken during the test period; oxygen consumption was also determined simultaneously, duplicate samples being used. In a third series, the sugar consumption was determined in the presence of 95 per cent oxygen and 95 per cent nitrogen, respectively, the conditions used by Warburg⁷ and other recent investigators of tissue metabolism.

Preparation of Suspensions of Leukocytes in Plasma.—The blood was withdrawn from an arm vein and immediately mixed with a small amount of a 2 per cent solution of heparin in 0.9 per cent sodium chloride (from 0.2 to 0.4 cc. per ten cubic centimeters of blood) to prevent clotting. The syringe was also wet with a small amount of the same solution before the blood was taken. In most cases the blood was then placed in long narrow test tubes (195 by 12 mm.) and centrifugated at low speed (from 1,200 to 1,400 revolutions per minute) for from ten to fifteen minutes, thus producing a layer of white blood cells above the mass of red blood cells. In case the separation was unsatisfactory, the upper layer of mixed white and red blood cells was pipetted off, resuspended in plasma and again centrifugated at low speed. Occasionally this procedure had to be repeated two or three times in order to obtain a suspension of leukocytes comparatively free from red blood cells. In making the suspensions, no Ringer's or citrate solution was employed, the blood plasma being used to dilute the cells to whatever volume was desired.

When the leukocyte count was low, separation was facilitated by centrifugation in tubes having a narrow neck at the point where the white blood cell layer

formed, the result being a thick layer of small diameter instead of a thin film spread out over the top of the red blood cell layer. This method has also been used by Endres.¹⁴ During the course of the investigation, it was found that in most leukemic blood specimens the white blood cells can be separated satisfactorily without centrifugation, simply by allowing the blood to stand in small test tubes (100 by 10 mm.) for an hour or less. This method has been used in the preparation of a few of the suspensions.

No precautions were taken to keep the blood and cell suspensions sterile, since there is abundant evidence¹⁵ that during short periods of incubation there is not enough bacterial growth in freshly drawn blood to have any appreciable effect on the metabolism.

The Determination of Number, Total Volume, Cell Size and Dry Weight of the Leukocytes.—The number of white blood cells and red blood cells per cubic millimeter of suspension was determined by counting. The percentage volume of the cells was found by means of a long narrow hematocrit tube (175 by 6.5 mm.), having a volume of 1 cc. and graduated in 0.01 cc. divisions. A cell volume as low as 1 per cent could be determined by means of this tube. Centrifugation was at the rate of 2,000 revolutions per minute for one-half hour.

The volume of the white blood cells was found by subtracting from the total cell volume the volume of the red blood cells. The latter was estimated from the red blood cell count by a simple calculation, it being assumed that 5,000,000 red blood cells have a volume of 45 per cent. This assumption is accurate enough for practical purposes when the number of red blood cells is comparatively small, as in our suspension.

By dividing the white blood cell volume, expressed in cubic millimeters per hundred cubic centimeters of suspension, by the cell count per cubic millimeter, a figure is obtained which represents the average cell volume. This figure is actually the volume of 100,000 white blood cells, and has been utilized for simplicity rather than the figure for the volume of a single cell.

Warburg and other recent investigators have expressed their results in terms of dry weight of tissue used. This has been done in a large number of the experiments of the present series. The dry weight of the leukocytes has been calculated as equal to one-fifth the volume.¹⁶ The direct determination of the dry weight of leukocytes suspended in plasma is difficult, since the weight may easily be altered during the process of washing them free from plasma.

In studying the metabolism of white blood cells in suspension, the blood platelets present have been neglected because, although their oxygen and sugar consumption per milligram are fairly large, as shown later in table 12, the total amount of these is insignificant on account of the small volume of the platelets (0.001 c. mm. per hundred thousand platelets). The volume of 100,000 blood platelets is equaled by that of only 1,300 normal white blood cells.

14. Endres, G.: Ein Verfahren zum Anreichern von weissen Blutkörperchen und Blutplättchen aus kleineren Blutmengen, *Klin. Wchnschr.* **6**:1407, 1927.

15. Macleod, J. J. R.: Blood Glycolysis: Its Extent and Significance in Carbohydrate Metabolism: The Supposed Existence of "Sucre Virtuel" in Freshly Drawn Blood, *J. Biol. Chem.* **15**:497, 1913. Tolstoi, E.: Glycolysis in Bloods of Normal Subjects and of Diabetic Patients, *J. Biol. Chem.* **60**:69, 1924. Cajori, F. A., and Crouter, C. Y.: A Comparison of the Rate of Glycolysis in Different Bloods with Special Reference to Diabetic Blood, *J. Biol. Chem.* **60**:765, 1924.

16. Warburg, O.: Versuche an überlebendem Carcinomgewebe (Methoden), *Biochem. Ztschr.* **142**:317, 1923.

Classification of the Blood Specimens and Suspensions According to the Degree of Maturity of the Leukocytes.—The blood specimens and suspensions were divided into three groups, according to the degree of maturity of the leukocytes. Group I comprises the bloods with the most mature cells, group III the bloods with the most immature cells, and group II is intermediate. Such groups cannot be rigidly defined, because each blood specimen shows peculiarities of its own, and the number and character of both typical and atypical cells must be taken into consideration in judging the picture of cell maturity or immaturity presented by each specimen. Nevertheless, it is seldom difficult to decide in which of these three broad groups a given blood specimen belongs.

Dr. George R. Minot has examined most of the stained smears made from the samples of blood used and assisted us in classifying them.

The classification is similar to that which was used in a study of the glycolysis of leukemic blood,¹¹ but it has been changed in some respects; group III of the present series comprising blood specimens with more immature cells than in the previous one. The essential point in this grouping is to classify the specimens according to the predominating group of cells, as these will exert the chief influence on the rate of metabolism.

The classification for myelogenous leukemia is as follows:

Group I: Bloods in which polymorphonuclear cells and metamyelocytes predominate, more immature cells being present in relatively low percentage.

Group II: Bloods in which the striking feature is the presence of myelocytes of all ages; polymorphonuclear cells and myeloblasts may be present in small numbers.

Group III: Bloods in which the immaturity of the cells is extreme. Specimens in this group contain 50 per cent or more of myeloblasts and premyelocytes (myelocyte A of Sabin and her associates¹⁷). Many of the cells are abortive in character.

The classification for lymphatic leukemia is similar.

Group I: Bloods in which the white blood cells are mostly normal small lymphocytes.

Group II: Bloods containing many medium and large lymphocytes.

Group III: Bloods with chiefly lymphoblasts and atypical lymphocytes, together with a few medium and large lymphocytes.

The same classification was used in grouping the suspensions of white blood cells prepared from leukemic blood specimens.

The Determination of Oxygen Consumption.—Oxygen consumption was determined by means of the apparatus of Wilbur, Daland and Cohen.¹⁸ This consists of a closed chamber containing the blood, connected with a water manometer and a potassium hydroxide absorption chamber, the whole being immersed in a water bath at 37 C. The air in the chamber with the blood is forced in and out of the potassium hydroxide absorption chamber, this procedure quickly freeing it from carbon dioxide. Thereafter, any change in the volume of the inclosed air, as registered by the manometer, is due to the consumption of oxygen by the blood

17. Cunningham, R. S.; Sabin, F. R., and Doan, C. A.: The Development of Leucocytes, Lymphocytes and Monocytes from a Specific Stem-Cell in Adult Tissues, Carnegie Institute of Washington, 1925, Pub. no. 361, p. 227.

18. Wilbur, B. C.; Daland, G. A., and Cohen, J.: Cell Respiration Studies: I. A Microspirometer for the Continuous Study of the Oxygen Absorption by Living Cells, J. Exper. Med. 46:43, 1927.

cells. A compensation chamber is attached in such a way that slight changes in temperature do not affect the reading of the manometer. A stirring device is also provided, which keeps the blood cells in gentle motion and prevents them from settling.

In the use of this apparatus certain points must be kept in mind. If whole blood is being studied, the red blood cells must first be fully saturated with oxygen, preferably before being introduced into the apparatus, in order that the taking up of oxygen by hemoglobin may not be confused with actual oxygen consumption by the cell protoplasm. In the case of blood specimens having a large number of actively respiring leukocytes, it is impossible for the blood to absorb oxygen fast enough to supply their needs, even if fairly vigorous stirring is employed. The result is that the red blood cells become partially desaturated, giving up their oxygen to the white blood cells. In such cases, which are not common, the observed oxygen consumption of the leukocytes is somewhat lower than the actual oxygen consumption since the oxygen abstracted from the red blood cells cannot be measured. In suspensions of white blood cells, the oxygen consumption is considerably lower than in specimens of whole blood containing a corresponding number of cells. This is caused, in part at least, by the fact that in the suspensions there are almost no red blood cells to take up oxygen and pass it along to the white blood cells. It is therefore advantageous to use whole blood rather than suspensions of leukocytes for the determination of oxygen consumption.

After the blood has been placed in the respiration chamber, a few minutes must be allowed for it to come to a relatively constant p_H . The free carbon dioxide present is rapidly abstracted, and at the same time the p_H rises. After this initial rise the p_H remains comparatively constant but tends gradually to fall again on account of the lactic acid which the white blood cells are constantly producing. The net result depends on the amount of lactic acid formed. The p_H , measured by the colorimetric method at the end of a number of the experiments, has varied between 7.6 and 8.3. Fortunately, such a variation has no great effect on the rate of oxygen consumption. Koehler and Reitzel,¹⁹ studying the effect of p_H on the oxygen consumption of blood and various tissues, obtained figures indicating that at a p_H of 8.3 there is a diminution of about 15 per cent as compared with a p_H of 7.4. We have performed a number of experiments that have yielded results similar to theirs.

The oxygen consumption of the erythrocytes is so much smaller than that of the leukocytes, provided the number of leukocytes is not below 20,000 per cubic millimeter, that it may be neglected, even in whole blood, and the entire oxygen consumption of the blood attributed to the white blood cells.

The oxygen consumption, per hour, of the blood or suspension of leukocytes, expressed as cubic centimeters per hundred cubic centimeters, divided by the leukocyte count expressed in thousands per cubic millimeter, gives the oxygen consumption per hour in cubic centimeters per $1,000 \times 10^5$ leukocytes. The oxygen consumption per hour expressed as cubic millimeters per cubic centimeter of suspension, divided by the dry weight of the leukocytes in a cubic centimeter of suspension (calculated from the hematocrit reading and expressed in milligrams), gives the oxygen consumption per hour in cubic millimeters per milligram of leukocytes. The symbol " Q_{O_2} " is used by Warburg⁷ to express this quantity.

The Determination of Sugar Consumption.—The experiments of the first series (tables 7, 8 and 9) were done by the following method. From 5 to 8 cc. of

19. Koehler, A. E., and Reitzel, R. J.: The Effect of p_H on the Oxygen Consumption of Tissues, *J. Biol. Chem.* 64:739, 1925.

leukocyte suspension was placed in a 50 cc. Erlenmeyer flask. After the removal of a 1 cc. sample for the determination of the initial concentration of sugar, the flask was stoppered tightly with cotton, rapidly warmed to 37 C. in a bath of warm water and then placed in an incubator at 37 C. Thereafter, 1 cc. samples were withdrawn for sugar determinations at one-half or one hour intervals, the protein-free filtrate being immediately prepared from each sample as soon as taken. The blood was not shaken, except when samples were removed for analysis. Protein-free filtrates were made by the method of Folin and Wu,²⁰ and sugar was determined by the method of Folin.²¹

The experiments of the second series (table 10) were performed in a similar manner except that the cells were kept in gentle motion by a device which tipped the containers from side to side about once in three seconds. Oxygen consumption was also determined simultaneously, with duplicate samples of suspension, by the method already described. Some of the sugar determinations were made by the method of Folin,²¹ and the remainder by the method of Folin and Wu.²²

In the third series (table 11), the sugar consumption was determined under "aerobic" and anaerobic conditions as used by Warburg, that is, in 95 per cent oxygen and 95 per cent nitrogen, respectively. Three or 4 cc. of leukocyte suspension was placed in a specially designed vessel having an inlet and an outlet tube, with stopcocks, so that the air within could be washed out and replaced by the gas mixture, the stopcocks being then closed so as to retain this. For aerobic conditions a mixture of 95 per cent oxygen and 5 per cent carbon dioxide was used; for anaerobic, 95 per cent nitrogen and 5 per cent carbon dioxide. The carbon dioxide in these mixtures served to keep the blood carbon dioxide at a physiologic level. The gas was passed through the chambers at a rapid rate for about five minutes to insure that the air was thoroughly washed out. The chambers were then placed in a water bath at 37 C. and allowed to remain there with gentle shaking for from forty to sixty minutes. Sugar determinations were done at the beginning (before the chambers were filled with gas), and again at the end of the experiment. In calculating the rate of sugar consumption, only the time while the chambers were in the water bath was used; the small amount of sugar consumption at room temperature during the filling of the chambers with gas mixture could be neglected. In order to prevent the sugar from being entirely used up during the course of the experiment, a small amount of pure dextrose (about 100 mg. per hundred cubic centimeters) was added to the suspension and thoroughly dissolved, a short time before the initial sample was taken for sugar determination. It was shown by control experiments (to be described) that this procedure did not affect the rate of sugar consumption.

The sugar consumption, per hour, expressed as milligrams of dextrose per hundred cubic centimeters, divided by the leukocyte count expressed in thousands per cubic millimeter, gives the sugar consumption per hour in milligrams per $1,000 \times 10^5$ leukocytes. The sugar consumption per hour, expressed as milligrams per hundred cubic centimeters, divided by the dry weight of leukocytes in 100 cc. of suspension (calculated from the hematocrit reading and expressed in milli-

20. Folin, O., and Wu, H.: A System of Blood Analysis, *J. Biol. Chem.* **38**: 81, 1919.

21. Folin, O.: The Determination of Sugar in Blood and in Normal Urine, *J. Biol. Chem.* **67**:357, 1926. Folin, O., and Svedberg, A.: The Sugar in Urine and in Blood, *J. Biol. Chem.* **70**:405, 1926.

22. Folin, O., and Wu, H.: A Simplified and Improved Method for Determination of Sugar, *J. Biol. Chem.* **41**:367, 1920.

grams), gives the sugar consumption in milligrams per milligram of leukocytes per hour.

A small fraction of the sugar utilized by the cells is probably oxidized. The remainder is converted into lactic acid,²³ a process requiring no oxygen. The term "glycolysis" is applied, in its narrower sense, only to the latter process. In most of the experiments the total sugar consumption has been determined, but in the series reported in table 10 the glycolysis has been calculated by deducting from the total sugar consumption the amount of sugar oxidized, it being assumed that all the oxygen consumed was used for this purpose. The amount oxidized is found by simple chemical calculation to be 0.00133 Gm. of dextrose per cubic centimeter of oxygen consumed. The glycolysis thus determined is on the average about 85 per cent of the total sugar consumption.

RESULTS

Oxygen Consumption.—The amount of oxygen consumed by blood from normal persons is so small that it cannot be measured satisfactorily by the methods used. This is due to the fact that the oxygen consumption of the red blood cells is extremely small, while the white blood cells, though actively respiring, are comparatively few in number. The results on twenty-two normal blood specimens are reported in a previous paper.¹⁰ Studies of blood specimens with increased white counts show that these have a considerably larger oxygen consumption. Several observations have been reported¹⁰ in the case of a patient with polymorphonuclear leukocytosis accompanying an infected tumor growth. The average amount of oxygen consumed by the blood from this case was 0.09 cc. per $1,000 \times 10^5$ white blood cells per hour.

The results of observations on blood specimens from cases of myelogenous and lymphatic leukemia are given in tables 1 and 2. As in leukocytosis, the oxygen consumption of the blood is due almost entirely to the white blood cells, that of the red blood cells being negligible in comparison. The data are arranged according to the maturity of the white blood cells. Some of the results recorded in table 1 (marked by an asterisk) were reported before,¹⁰ but not with the present method of grouping.

A study of the metabolism of blood from cases of myelogenous leukemia (table 1) shows that the more mature white blood cells have a higher rate of oxygen consumption than the immature cells. In group 1, the most mature group, polymorphonuclear leukocytes and metamyelocytes were the predominating cells. The values for oxygen consumption ranged from 0.155 to 0.084 cc. per $1,000 \times 10^5$ white blood cells per hour. In group II, the intermediate group, the oxygen consumption ranged from 0.079 to 0.041 cc. In group III, characterized by the extreme immaturity of the white blood cells, the values were lowest of all, from 0.049 to 0.035 cc. The average rates for the three groups were 0.101, 0.060 and 0.043 cc., respectively. Thus there was

23. Fleischmann and Kubowitz (footnote 8, second reference).

a definite correlation between the maturity of the white blood cells and their rate of oxygen consumption.

The cases in group III merit further description on account of their unusual interest. The patients R. T. and L. S. were in a period of acute exacerbation marking the terminal stages of the disease, the duration of which was known to have been at least two and one-half years and one and one-half years, respectively. The blood of R. T., at this time, showed more than 50 per cent myeloblasts, many of which were atypical. Many megakaryocytes were present, with masses of blood platelets. The blood of L. S. showed 52 per cent myeloblasts and 42 per cent myelocytes; many of the latter were very young. There

TABLE 1.—*Oxygen Consumption of Blood in Myelogenous Leukemia*

Patient	Date	White Blood Cells per C.Mm.	Red Blood Cells per C.Mm.	Oxygen Consumed per Hour per		Degree of Maturity of White Blood Cells, Group*
				100 Cc. of Blood, Cc.	1,000 $\times 10^5$ White Blood Cells, Cc.	
W. D.....	9/29/28	63,000	4,400,000	9.76	0.155	I
A. N.....	9/20/28	48,000	4,000,000	4.90	0.102	I
K. G.*.....	1/12/26	80,000	4,000,000	6.46	0.081	I
C. L.*.....	10/ 5/26	53,000	3,800,000	3.84	0.072	I
F. N.*.....	12/17/25	37,000	2,800,000	4.48	0.121	I
G. S.*.....	12/18/25	123,000	3,100,000	12.67	0.103	I
S. L.*.....	12/12/25	71,000	2,200,000	6.14	0.086	I
W. D.....	12/15/29	91,000	2,800,000	7.66	0.084	I
				Average 0.101		
S. L.*.....	12/ 8/25	122,000	3,200,000	9.72	0.079	II
P. S.....	9/13/28	128,000	3,400,000	8.56	0.067	II
S. H.....	9/25/28	200,000	3,500,000	11.71	0.059	II
F. N.*.....	4/ 7/26	112,000	4,100,000	5.89	0.053	II
S. H.*.....	10/13/26	454,000	3,000,000	18.56	0.041	II
				Average 0.060		
W. G.....	12/ 8/28	210,000	3,600,000	9.42	0.045	III
B. O.....	7/ 9/29	49,000	2,800,000	2.38	0.049	III
R. T.*.....	10/21/26	176,000	3,100,000	7.30	0.041	III
L. S.*.....	2/ 4/26	251,000	2,900,000	8.77	0.035	III
				Average 0.043		

* For explanation of group see text.

were practically no blood platelets. W. G. had a much more acute type of the disease. He had had symptoms for only six weeks prior to the date of the test. The differential count of the white blood cells showed 10.5 per cent polymorphonuclear cells, 30 per cent myelocytes and 62.5 per cent of primitive white blood cells or myeloblasts. Patient B. O. had a lower count than the others, but between 70 and 80 per cent of the cells were myeloblasts. Many of these were pathologic forms with vacuoles. A specimen submitted to the oxidase stain showed some granular cells, but these were hard to demonstrate either with Wright's stain or by supravital studies.

In lymphatic leukemia, as in myelogenous leukemia, the blood specimens with mature cells showed a much greater oxygen consumption

TABLE 2.—Oxygen Consumption of Blood in Lymphatic Leukemia

Patient	Date	White Blood Cells per C.Mm.	Red Blood Cells per C.Mm.	Oxygen Consumed per Hour per		Degree of Maturity of White Blood Cells, Group
				100 Cc. of Blood, Cc.	1,000×10 ⁵ White Blood Cells, Cc.	
C. O.....	11/ 8/28	53,000	4,100,000	6.0	0.113	I
L. G.....	7/19/28	58,000	3,200,000	6.2	0.107	I
K. N.....	2/11/29	156,000	2,700,000	6.2	0.040	I
				Average 0.087		
B. N.....	10/ 3/28	91,000	4,600,000	5.4	0.059	II
W. Y.....	12/ 3/28	109,000	3,200,000	5.7	0.052	II
M. T.....	12/ 7/28	172,000	1,200,000	8.8	0.051	II
				Average 0.054		
T. R.....	7/ 8/29	3,300,000	0.95	0.013	III
G. N.....	5/ 7/29	75,000	1,300,000	0.85	0.011	III
				Average 0.012		

TABLE 3.—Oxygen Consumption of Suspensions of White Blood Cells from Cases of Myelogenous Leukemia

Patient	Date	White Blood Cells per C.Mm.	Volume of White Blood Cells, per Cent	Red Blood Cells, per C.Mm.	Oxygen Consumed per Hour per			Degree of Matur- ity of White Blood Cells, Group
					100 Cc. of Susten- sion, Cc.	1,000 ×10 ⁵ White Blood Cells, Cc.	Mg. of White Blood Cells, C.Mm.	
G. S.	7/20/26	115,000	9.6	65,000	2.72	0.024	1.4	I
S. S.	3/21/28	112,000	5.8	154,000	2.99	0.027	2.6	I
W. H.	9/27/27	222,000	15.0	270,000	5.24	0.024	1.8	I
S. L.	7/14/27	134,000	7.9	224,000	5.62	0.042	3.6	I
				Av. 0.029		Av. 2.3		
S. S.	3/23/28	121,000	6.8	273,000	5.09	0.042	3.7	II
S. L.	11/26/26	165,000	137,000	4.99	0.030	...	II
S. L.	12/13/26	232,000	121,000	3.95	0.017	...	II
S. A.	12/ 8/27	89,000	4.7	380,000	1.90	0.021	2.0	II
E. N.	11/23/26	265,000	80,000	3.68	0.014	...	II
A. Y.	9/22/27	274,000	256,000	6.99	0.026	...	II
M. S.	7/22/28	180,000	13.6	25,000	6.23	0.035	2.3	II
G. L.	9/20/27	171,000	12.2	260,000	4.99	0.029	2.1	II
M. K.	7/15/27	703,000	32.6	426,000	7.04	0.010	1.1	II
S. H.	10/15/26	74,000	8.6	140,000	3.63	0.049	2.1	II
S. H.	5/27/27	477,000	4.99	0.010	...	II
S. H.	12/ 2/27	86,000	5.5	214,000	0.95	0.011	0.9	II
B. M.	3/15/28	100,000	7.0	103,000	5.71	0.057	4.1	II
H. Y.	10/18/28	136,000	9.7	35,000	2.38	0.018	1.2	II
				Av. 0.026		Av. 2.2		
P. W.	3/ 7/28	247,000	9.0	26,000	5.24	0.021	2.9	III
P. T.	7/21/27	124,000	9.4	90,000	5.33	0.043	2.8	III
R. T.	12/16/26	255,000	86,000	4.54	0.018	...	III
R. N.	10/ 8/27	125,000	3.7	44,000	3.90	0.031	5.3	III
R. N.	11/ 1/27	110,000	4.8	39,000	3.57	0.032	3.7	III
C. Y.	2/23/28	99,000	6.9	84,000	2.19	0.022	1.6	III
				Av. 0.027		Av. 3.2		

than those with many immature cells, as shown in table 2. In group I, two cases showed very high rates, 0.113 and 0.107 cc., respectively, per $1,000 \times 10^5$ white blood cells per hour. These were about twice the values in the intermediate group (0.059, 0.052 and 0.051 cc.) and nearly ten times the values for the bloods of group III, with many very immature cells (0.013 and 0.011 cc.).

The cases in group III deserve comment. The differentiation between very immature cells of the lymphatic and myelogenous types is

TABLE 4.—*Oxygen Consumption of Suspensions of White Blood Cells from Cases of Lymphatic Leukemia*

Patient	Date	White Blood Cells per C.Mm.	Volume of White Blood Cells, per Cent	Red Blood Cells, per C.Mm.	Oxygen Consumed per Hour per			Degree of Matur- ity of White Blood Cells, Group
					100 Cc. of Suspension, Cc.	$1,000 \times 10^5$ White Blood Cells, Cc.	Mg. of White Blood Cells, C.Mm.	
K. N.	7/11/27	290,000	6.7	30,000	4.76	0.016	3.6	I
B. N.	4/22/27	1,618,000	92,000	4.99	0.003	...	I
B. N.	5/17/27	971,000	14,000	5.67	0.006	...	I
B. N.	7/20/27	151,000	3.7	58,000	4.52	0.030	6.1	I
B. N.	6/27/28	232,000	5.3	192,000	6.90	0.030	6.5	I
B. N.	10/ 3/28	136,000	3.0	16,000	7.28	0.054	12.1	I
K. N.	4/20/27	354,000	24,000	2.67	0.008	...	I
B. S.	12/20/26	445,000	40,000	4.76	0.011	...	I
B. S.	12/22/26	241,000	8,000	2.72	0.011	...	I
A. G.	7/ 5/28	1,095,000	24.6	91,000	10.71	0.010	2.2	I
Av. 0.018								
J. G.	4/16/28	680,000	14.6	21,000	6.90	0.010	2.4	II
G. R.	4/28/27	155,000	116,000	1.81	0.012	...	II
M. N.	4/21/27	177,000	92,000	2.13	0.012	...	II
M. N.	7/ 8/27	340,000	8.6	41,000	4.76	0.014	2.8	II
W. Y.	12/ 1/26	265,000	17,000	3.86	0.015	...	II
W. Y.	4/11/27	430,000	11,000	4.09	0.010	...	II
W. Y.	7/ 6/28	46,000	1.5	108,000	5.09	0.110	17.0	II
Av. 0.026								
W. F.	7/20/28	298,000	12.2	142,000	6.80	0.023	2.8	III
W. F.	7/20/28	281,000	11.5	24,000	8.37	0.030	3.6	III
M. Y.	11/11/26	79,000	10,000	0.91	0.012	...	III
Av. 0.022								

difficult, but in both cases (T. R. and G. N.) reported here the diagnosis of lymphatic leukemia was free from doubt. Both patients showed moderate enlargement of the lymph nodes as well as of the spleen and liver. Earlier observations had shown typical blood pictures of chronic lymphatic leukemia with many mature lymphocytes, but at the time of our experiments the cells were very immature, so that lymphoblasts and atypical large lymphocytes predominated. There was, in addition, a severe anemia and thrombopenia. Both patients died within a month after the tests reported here were made.

The values for oxygen consumption per $1,000 \times 10^5$ white blood cells averaged somewhat lower for the blood specimens of the patients with lymphatic leukemia than for those of the patients with myelogenous

leukemia. This difference was no doubt due to the smaller size of the lymphatic cells.

Suspensions of white blood cells in plasma were also used for the determination of oxygen consumption. The results obtained are shown in tables 3, 4 and 5. Cells from normal blood from patients with polymorphonuclear leukocytosis and from cases of myelogenous and lymphatic leukemia were studied in this way.

In tables 3 and 4 the suspensions are listed in groups according to the maturity of the cells, in the same manner as was done for the specimens of whole bloods recorded in tables 1 and 2. In contrast to the latter specimens, however, the suspensions showed no relationship

TABLE 5.—*Oxygen Consumption of Suspensions of Normal White Blood Cells*

Name	White Blood Cells, per C. Mm.	Volume of White Blood Cells, Per Cent	Red Blood Cells, per C. Mm.	Oxygen Consumption per Hour per		
				100 Ce. of Suspension, Ce.	1,000×10 ⁵ White Blood Cells, Ce.	Mg. of White Blood Cells C. Mm.
White Blood Cells from Normal Subjects						
W. S.	36,000	2.6	164,000	1.90	0.053	3.7
E. V.	28,000	2.9	207,000	2.86	0.102	4.9
E. S.	43,000	3.4	214,000	4.52	0.105	6.7
B. D.	28,000	2.8	432,000	2.95	0.105	5.3
H. S.	18,000	1.3	34,000	2.71	0.151	10.4
M. L.	19,000	1.9	487,000	3.76	0.198	9.9
				Av. 0.119		
White Blood Cells from Patients with Polymorphonuclear Leukoeytosis						
B. R.	67,000	...	1,500,000	1.59	0.024
W. P.	113,000	...	1,055,000	4.54	0.040
C. N.	74,000	7.0	1,310,000	3.09	0.042	2.2
A. N.	42,000	...	388,000	2.72	0.065
H. T.	44,000	...	377,000	3.18	0.072
A. N.	70,000	...	730,000	6.81	0.097
P. O.	13,000	1.8	198,000	1.43	0.110	4.0
				Av. 0.064		

between the degree of maturity of the cells and the rate of oxygen consumption.

The rates of oxygen consumption by the cells in these suspensions were definitely lower than the rates obtained by the use of whole blood, as shown in table 6. The rates were about the same in the suspensions of white blood cells from myelogenous and lymphatic leukemia. Both were much lower (0.027 and 0.021 cc.) than the rates in suspensions of normal white blood cells (0.119 and 0.064 cc.).

There are several reasons that may account for the lower rates of oxygen consumption in cell suspensions than in whole blood and for the lack of correlation between the maturity of the cells and the oxygen consumption. In the first place, the white blood cells in the suspensions were not as well supplied with oxygen. In the specimens of whole blood, the red blood cells, with their strong affinity for oxygen, were constantly absorbing it from the air and thus keeping the blood saturated, except in a few cases in which the oxygen consumption of the

white blood cells was so rapid that even the red blood cells could not keep pace with it and became desaturated. It is evident that in suspension the supply of oxygen must have been much smaller. A few red blood cells were present in the suspensions, but their effect was apparently negligible, and the rates of oxygen consumption appeared in no way dependent on their number.

Slight degrees of injury due to manipulation of the cells for preparation of the suspensions probably exerted a marked effect on their oxygen consumption. Thus Fujita⁹ noted that the oxygen consumption of leukocytes could be markedly lowered by centrifugation. It is of interest that the leukemic white blood cells, even of mature type, showed much lower rates than the normal white blood cells. This may have been due, in part at least, to a greater susceptibility of the leukemic cells to injury. Szilard²⁴ has shown that the fragility of leukemic white blood cells is greater than that of normal cells when incubated in serum or

TABLE 6.—Rate of Oxygen Consumption

Diagnosis	Average Rate per 1,000×10 ⁵ White Blood Cells	
	Whole Blood, Cc.	Suspension, Cc.
Normal	0.119
Leukocytosis	0.09	0.064
Myelogenous leukemia	0.075	0.027
Lymphatic leukemia	0.056	0.021

plasma. The frequent occurrence of broken cells in smears of leukemic blood likewise indicates an abnormal degree of fragility.

In the preparation of the suspensions, the blood specimens were centrifugated slowly in order to reduce cell trauma to a minimum. Such cell suspensions have been observed to use oxygen continually at a constant rate for from four to five hours, a fact which indicates that the cells could not have been seriously injured. Furthermore, stained smears prepared from the suspensions at the end of the experiments showed the leukocytes to be in excellent condition, and supravital studies showed the polymorphonuclear cells still motile, although not as active as at the beginning of the experiments.

It seems evident, therefore, that a slight amount of manipulation can exert a profound effect on the oxygen consumption of the white blood cells.

Sugar Consumption.—It was necessary first to determine whether or not the amount of sugar present in the cell suspension had any effect on the rate of sugar consumption. Warburg⁷ reported that in the case of tissues the concentration of sugar in the surrounding fluid exerts a marked influence on the rate of consumption. Conflicting

24. Szilard, P.: Studies on Leukemia: I. Concerning the Fragility of the White Blood Cells, *Am. J. M. Sc.* **173**:343, 1927.

results have been obtained with whole blood, some investigators²⁵ finding that the higher the sugar concentration the more rapidly it is destroyed, others²⁶ finding an opposite relationship, while the weight of opinion²⁷ is that the rate of consumption in blood is independent of the sugar concentration. Our own experiments with whole blood¹² were in agreement with the last view. Table 7 shows the results of four experiments in which varying amounts of pure dextrose were added to white blood cell suspensions and the rates of sugar consumption at the different concentrations compared. It was found that the added dextrose had practically no effect on the rate of consumption. Furthermore, in numerous experiments the rate was followed at successive half hour or one hour intervals and found to remain constant as long as there was any sugar left. The rate of sugar consumption is independent of the concentration of sugar, at least up to a concentration of 250 mg. per hundred cubic centimeters.

TABLE 7.—*Effect on Sugar Consumption of Varying the Initial Concentration of Sugar*

Patient	Type of Leukemia	Initial Sugar Concentration		Sugar Consumption per 100 Cc. of White Blood Cell Suspension per Hour	
		Suspension 1 Mg. per 100 Cc.	Suspension 2 Mg. per 100 Cc.	Suspension 1 Mg.	Suspension 2 Mg.
G. R.	Lymphatic	133	210	5	5
S. H.	Myelogenous	182	246	18	22
K. N.	Lymphatic	142	218	36	35
B. N.	Lymphatic	134	226	55	52

Another series of experiments was performed to determine whether the rate per $1,000 \times 10^5$ cells was the same in suspensions having a high cell count as in more dilute suspensions of the same cells. There was some possibility that crowding of the cells in the more concentrated suspensions might cause a falling off in the rate of sugar consumption. The results shown in table 8 demonstrate that this is not the case. In parallel suspensions varying from two to eight times in the concentration of cells the rates of sugar consumption per $1,000 \times 10^5$ cells were remarkably constant with but one exception.

As a result of these preliminary experiments it was believed that the rates of sugar consumption obtained with different suspensions might

25. Falcon-Lesses (footnote 12). Cajori and Crouter (footnote 15, third reference).

26. Levene, P. A., and Meyer, G. M.: The Action of Leucocytes on Glucose, J. Biol. Chem. **11**:361, 1912. Lemann, I. I., and Liles, R. T.: Glycolysis at Varying Blood Sugar Levels, J. Lab. & Clin. Med. **11**:339, 1926.

27. Denis, W., and Giles, U.: On Glycolysis in Diabetic and Non-Diabetic Blood, J. Biol. Chem. **56**:739, 1923. Macleod (footnote 15, first reference). Irving, J. T.: The Degradation of Glucose by the Blood Corpuscle of the Rabbit. Biochem. J. **20**:613, 1926.

be safely compared without the occurrence of any significant error due to varying concentrations of sugar or of cells.

Table 9 shows strikingly the relationship of the maturity of the white blood cells to the rate of sugar consumption. The experiments of this first series were done without agitation of the cells. Of the myelogenous cells, the most mature (group I) showed the lowest sugar consumption, from 0.16 to 0.39 mg. per $1,000 \times 10^5$ white blood cells per hour. Those of moderate immaturity (group II) showed higher rates, from 0.42 to 0.76 mg. per hour, while the most immature cells (group III) had by far the highest rate, 0.93 mg. per hour. Similar but much lower figures were obtained with the lymphatic white blood cells, ranging from 0.082 mg. per $1,000 \times 10^5$ cells per hour in group I to 0.256 mg. in group III. White blood cells obtained from normal blood were also studied in three experiments. Since these were mature

TABLE 8.—*Effect on Sugar Consumption of Varying the Concentration of White Blood Cells*

Patient	Type of Leukemia	White Blood Cells per C. Mm.			Sugar Consumption per $1,000 \times 10^5$ White Blood Cells per Hour	
		Suspension 1	Suspension 2	Ratio of White Blood Cell Counts	Suspension 1, Mg.	Suspension 2, Mg.
B. S.	Lymphatic	61,000	122,000	2.0	0.09	0.10
W. Y.	Lymphatic	74,000	148,000	2.0	0.13	0.13
B. N.	Lymphatic	299,000	749,000	2.5	0.08	0.07
G. D.	Myelogenous	39,500	239,000	6.0	0.55	0.42
G. R.	Lymphatic	23,500	141,000	6.0	0.17	0.15
S. H.	Myelogenous	23,500	188,000	8.0	0.77	0.76

cells, predominantly of the myelogenous type, it was expected that their rate of sugar consumption would resemble that of the most mature cells of myelogenous leukemia. Surprisingly enough, it was much higher, from 0.64 to 0.79 mg. per $1,000 \times 10^5$ cells per hour, being distinctly greater even than the average rate for the moderately immature myelogenous cells of group II.

A series of more elaborate experiments is reported in table 10. In these experiments the cells were kept in better equilibrium with the surrounding plasma by constant gentle agitation. Oxygen consumption was determined simultaneously with sugar consumption. The values for oxygen consumption have already been given in tables 3, 4 and 5, but are inserted in table 10 also, for purposes of comparison. It is to be noted that glycolysis, rather than total sugar consumption, is reported in table 10. The amount of sugar presumably oxidized has been subtracted from the total amount of sugar consumed, leaving the amount changed to lactic acid, or glycolized. The results given in tables 10 and 11 are expressed in milligrams of sugar per milligram of cells, instead of in milligrams per $1,000 \times 10^5$ cells. The results are

thus independent of the size of the cells, which is variable as shown in the column giving the volume of 10^5 white blood cells. Cells of both myelogenous and lymphatic type are listed together in order to bring out the fact that, so far as the evidence goes, the rates of glycolysis per milligram are approximately the same in both types of cells of the same degree of maturity. The lower rates shown in table 9 for cells of the lymphatic type were evidently due entirely to the smaller size of the cells. The white blood cells in group III (table 10) were taken from

TABLE 9.—*Sugar Consumption of White Blood Cells (First Series) 37 C., No Shaking*

Patient	Date	White Blood Cells, per C.Mm.	Red Blood Cells, per C.Mm.	Sugar Consumption per $1,000 \times 10^5$ White Blood Cells per Hour, Mg.	Degree of Maturity of White Blood Cells, Group
Myelogenous Leukemia					
G. S.	7/19/26	159,000	170,000	0.16	I
S. L. (1).....	11/26/26	104,000	28,000	0.20	I
S. L. (2).....	9/ 3/26	72,000	40,000	0.39	I
S. H. (1).....	10/16/26	308,000	225,000	0.42	II
F. N.	10/19/26	89,000	125,000	0.47	II
G. D. (1)	1/29/27	38,000	48,000	0.57	II
G. D. (2)	1/28/27	90,000	85,000	0.70	II
S. H. (2)	5/ 3/27	188,000	117,000	0.76	II
C. L.	12/23/26	20,000	2,000	0.93	III
Lymphatic Leukemia					
B. N.	4/22/27	299,000	17,000	0.082	I
M. O. (1)	11/27/26	57,000	22,000	0.086	I
K. R. (1)	8/ 3/26	71,000	18,000	0.089	I
K. N. (1)	11/29/26	154,000	10,000	0.094	I
M. O. (2)	11/16/26	122,000	50,000	0.097	I
B. S.	12/22/26	122,000	4,000	0.102	I
K. N. (2)	4/20/27	325,000	22,000	0.109	I
K. R. (2)	7/26/26	212,000	55,000	0.113	I
W. Y.	12/ 1/26	148,000	12,000	0.125	I+
H. E.	7/21/26	30,000	65,000	0.147	I+
M. N.	9/24/26	98,000	14,000	0.159	II
G. R.	4/28/27	141,000	106,000	0.162	II
M. Y.	11/11/26	49,000	11,000	0.256	III
Normal					
G. R. (1)	12/ 2/26	4,800	8,600	0.64	...
G. R. (2)	3/24/27	39,000	89,000	0.61	...
M. N.	4/ 5/27	48,000	90,000	0.79	...

patients having acute leukemia. They were for the most part very primitive cells, and it was impossible to determine with certainty whether they were of myelogenous or of lymphatic origin.

The inverse relationship of glycolysis to the maturity of the white blood cells is clearly shown in table 10, though some irregularities are to be noted. Thus the cells of patient S. S., in group I, showed a glycolysis as high as would be expected in group III. The rates for group II showed a remarkably wide range of variation, from 0.018 to 0.045 mg. of sugar per milligram of cells per hour. It has already been stated that the oxygen consumption, which shows a direct relationship to the maturity of the cells when determined in whole blood, shows no

such relationship when determined in suspensions of the white blood cells. This is apparently due to injury of the cells during centrifugation and other manipulations employed in preparing the suspensions. Probably the similar but much less marked variability in the glycolysis of suspensions of white blood cells is also due to slight but varying degrees of cell injury.

TABLE 10.—*Glycolysis and Oxygen Consumption of White Blood Cells (Second Series) 37 C., Gentle Agitation*

Patient	Date	Type of Leukemia	White Blood Cells per C. Mm.	Volume of 10 ⁵ White Blood Cells, C. Mm.	Red Blood Cells per C. Mm.	Glycolysis per Mg. per Hour	Oxygen Consumption per Mg. per Hour	Degree of Maturity of White Blood Cells, Group
K. N.	7/11/27	Lymphatic	290,000	0.024	30,000	0.014	3.6	I
S. L.	7/14/27	Myelogenous	134,000	0.059	224,000	0.016	3.6	I
A. G.	7/ 5/28	Lymphatic	1,095,000	0.022	91,000	0.019	2.2	I
B. N.	6/27/28	Lymphatic	232,000	0.023	192,000	0.020	6.5	I
B. N.	7/20/27	Lymphatic	151,000	0.024	58,000	0.022	6.1	I
S. S.	3/21/28	Myelogenous	112,000	0.052	154,000	0.046	2.6	I
Av. 0.023								
M. N.	7/ 8/27	Lymphatic	340,000	0.025	41,000	0.018	2.8	II
M. K.	7/15/27	Myelogenous	703,000	0.046	426,000	0.021	1.1	II
W. Y.	7/ 6/28	Lymphatic	46,000	0.033	108,000	0.024	16.9	II
O. L.	9/20/27	Myelogenous	171,000	0.072	260,000	0.025	2.1	II
J. G.	4/16/28	Lymphatic	680,000	0.022	21,000	0.030	2.4	II
B. M.	3/14/28	Myelogenous	100,000	0.070	103,000	0.042	4.1	II
M. S.	7/22/27	Myelogenous	180,000	0.076	25,000	0.045	2.3	II
Av. 0.029								
H. S.	11/ 4/27	Acute, ? type	107,000	0.060	64,000	0.042±	...	III
P. W.	3/ 7/28	Acute, ? type	247,000	0.036	26,000	0.043	2.9	III
P. T.	7/21/27	Acute, ? type	124,000	0.076	90,000	0.044	2.8	III
C. A.	2/23/28	Acute, ? type	99,000	0.069	84,000	0.050	1.6	III
Av. 0.045								
Normal White Blood Cells								
B. D.	6/19/28		28,000	0.102	432,000	0.027	7.0	
M. L.	6/21/28		19,000	0.098	487,000	0.032	9.9	
W. S.	6/22/28		36,000	0.073	164,000	0.042	3.7	
E. S.	6/26/28		43,000	0.080	214,000	0.037	6.7	
E. V.	6/28/28		28,000	0.104	207,000	0.039	4.9	
H. S.	6/29/28		18,000	0.074	34,000	0.031	10.4	
Av. 0.035								

With but one exception, the rates of glycolysis for cells of group I were not above 0.022 mg. per hour, while the rates for group III were not below 0.042 mg. per hour.

The average rate of glycolysis for cells of group I was 0.023 mg. per milligram per hour, for group II, 0.029 mg. and for group III, 0.045 mg. The glycolysis of white blood cells obtained from normal healthy subjects was again surprisingly high, 0.035 mg., or distinctly above the average for cells from cases of myelogenous leukemia placed in group II.

In table 11 are shown the results obtained by measuring the sugar consumption of suspensions of white blood cells in 95 per cent oxygen and 95 per cent nitrogen respectively, the aerobic and anaerobic con-

ditions used by Warburg ⁷ and his collaborators and by Fujita.⁹ White blood cells from patients with myelogenous and lymphatic leukemia and from persons with normal blood were thus tested. In 95 per cent nitrogen, the sugar consumption of the cells was about the same for all types of leukemic cases so that there was no relationship to the maturity of the cells. In 95 per cent oxygen, however, marked differences appeared. In the cases of myelogenous leukemia, the rates of sugar consumption were much higher for suspension containing chiefly mature cells. This is directly opposed to the results obtained when the cell suspensions were

TABLE 11.—*Sugar Consumption of White Blood Cells in Oxygen and in Nitrogen 37 C., Gentle Agitation*

Patient	Date	White Blood Cells per C.Mm.	Volume of 10 ⁵ White Blood Cells, C.Mm.	Red Blood Cells per C.Mm.	Sugar Consumption per Mg. per Hour in		Degree of Matur- ity of White Blood Cells, Group
					95% O ₂ , 5% CO ₂ , Mg.	95% N ₂ , 5% CO ₂ , Mg.	
Myelogenous Leukemia							
P. S.....	11/23/28	91,000	0.036	23,000	0.103	0.073	I
W. D.....	12/15/28	68,000	0.082	40,000	0.066	0.079	I
S. G.....	3/22/29	198,000	0.069	42,000	0.056	0.068	II
B. D.....	1/.. /29	442,000	0.074	156,000	0.030	0.033	II
W. G.....	12/ 8/28	189,000	0.051	43,000	0.013	0.059	III
W. G.....	12/11/28	121,000	0.046	5,000	0.013	0.082	III
W. G.....	1/ 3/29	197,000	0.045	700,000	0.011	0.063	III
B. O.....	7/10/29	71,000	0.054	6,000	0.008	0.079	III
Lymphatic Leukemia							
K. N.....	2/11/29	179,000	0.023	0.009	0.059	I
W. Y.....	12/ 3/28	111,000	0.026	12,000	0.000	0.067	II
M. T.....	12/ 7/28	107,000	0.012	44,000	0.016	0.081	II
G. N.....	5/ 7/29	69,000	0.029	13,000	0.000	0.057	III
T. R.....	7/ 8/29	221,000	0.028	172,000	0.012	0.070	III
Normal							
M. Y.....	1/ 2/29	64,000	0.061	185,000	0.054	0.046	...
J. S.....	5/ 9/29	22,000	0.047	40,000	0.052	0.052	...
S. L.....	5/15/29	34,000	0.035	48,000	0.060	0.067	...

exposed to air. In the cases of lymphatic leukemia the cells of all degrees of maturity, even including the mature lymphocytes of case K. N., showed a very low sugar consumption in the presence of 95 per cent oxygen. Three suspensions of white blood cells from patients with normal blood showed a behavior similar to that of the more mature cells from cases of myelogenous leukemia, in that the rates of sugar consumption were about the same in both oxygen and nitrogen.

The metabolism of blood platelets was also studied in a suspension containing 1,001,000 blood platelets per cubic millimeter, and only 3,000 white blood cells and 1,500 red blood cells per cubic millimeter. This suspension was prepared from the blood of a patient with myelogenous leukemia with an exceptionally large number of blood platelets. Glycolysis was determined in air and in pure nitrogen, conditions

similar to those used by Endres and Kubowitz²⁸ for the study of blood platelets. In table 12 our results are compared with those of Endres and Kubowitz for the blood platelets of human beings and with those of Fujita⁹ for the blood platelets of rats. Our figures do not show the marked difference between aerobic and anaerobic glycolysis which they found, the metabolism being similar to that of normal white blood cells.

COMMENT

The foregoing results indicate a definite relationship between the metabolism of white blood cells from cases of leukemia and the degree of their maturity. As the cells develop from primitive types to adult forms, the consumption of oxygen becomes steadily greater, while the transformation of dextrose into lactic acid becomes correspondingly less. The white blood cells are susceptible to injury, so that in the process of separating them from the red blood cells by centrifugation their oxygen consumption, and, to a lesser degree, their sugar con-

TABLE 12.—*Glycolysis and Oxygen Consumption of Blood Platelets*

Authors	Aerobic Glycolysis per Mg. per Hour, Mg.	Anaerobic Glycolysis per Mg. per Hour, Mg.	Oxygen Con- sumption per Mg. per Hour, C.Mm.	Volume of 10 ⁵ Platelets, C.Mm.
Glover, Daland and Schmitz.....	0.040	0.058	7.5	0.001
Endres and Kubowitz ²⁸	0.021	0.084	8.4
Fujita ⁹	0.004	0.100	6.2

sumption is altered. For this reason the correlation between oxygen consumption and the age of the cells is not demonstrable by a study of cell suspensions but only by observations on cells in whole blood; likewise, the correlation between sugar consumption and maturity though clearly indicated is not perfect in cell suspensions.

Many of the patients whose blood was studied had received high voltage (170,000 volts) roentgen treatments at times varying from days to months previous to our tests. Blood was not taken during the first few hours after treatment, but after this period the metabolism of the cells appeared to be no different from that of cells of the same degree of maturity from untreated patients.

There is no fundamental difference between the metabolism of leukemic white blood cells and that of normal white blood cells. The normal cells, however, show a more active metabolism than do cells of corresponding maturity in leukemic blood, as regards both oxygen and sugar consumption.

28. Endres, G., and Kubowitz, F.: Stoffwechsel der Blutplättchen, Biochem. Ztschr. **191**:395, 1927.

Warburg ⁷ has demonstrated important differences in the metabolism of different types of tissue, which may be summarized as follows:

	Oxygen Consumption	Aerobic Glycolysis	Anaerobic Glycolysis
Normal adult tissue.....	Moderate	Small	Small
Embryonic tissue	Moderate	Small	Large
Malignant tumors	Moderate	Large	Large

He and others have recognized that this classification is not absolute, the most notable exceptions being the retina and the white blood cells.²⁹

Furthermore, there is considerable variation in the metabolic activity even of tumors. Some malignant tumors, for example, have a metabolism similar to that of benign tumors, according to Warburg's classification, as demonstrated by Murphy and Hawkins.³⁰ Hawkins ³¹ concluded that the anaerobic glycolytic activity of tissues is a function of their growth rate.

Typical results obtained by other investigators for the metabolism of leukocytes are given in table 13. The figures for glycolysis have

TABLE 13.—Metabolism of Leukocytes as Determined by Other Investigators

Authors	Description of Leukocytes	Oxygen Con- sumption per Mg. per Hour, C.Mm.	Aerobic Glycolysis per Mg. per Hour, Mg.	Anaerobic Glycolysis per Mg. per Hour, Mg.
Bakker ²⁹	Exudate leukocytes of rabbits	0.4	0.017
Fleischmann and Kubowitz ²³	Exudate leukocytes of rabbits	4.5	0.056	0.084
.....	Blood leukocytes of geese....	4.4	0.007	0.046
Fujita ⁹	Blood leukocytes of rats.....	9.1	0.009	0.082
.....	Bone-marrow cells of rats...	9.8	0.015	0.084

been recalculated from the original figures, in which the amount of glycolysis was represented by the volume of carbon dioxide liberated by the formation of lactic acid. The results obtained by Bakker were much lower than the rest. The metabolism of exudate leukocytes obtained from rabbits by Fleischmann and Kubowitz ²³ resembled that of malignant tissue, whereas the metabolism of blood leukocytes of geese and of rats and of bone-marrow cells of rats resembled that of embryonic tissue. The results of our own experiments under aerobic and anaerobic conditions (table 11) interpreted in the same way are as follows: Normal white blood cells and mature cells from cases of myelogenous leukemia resembled malignant tissue in their metabolism; immature cells from cases of myelogenous leukemia, and both mature

29. Bakker (footnote 8, first reference).
30. Murphy, J. B., and Hawkins, J. A.: Comparative Studies on the Metabolism of Normal and Malignant Cells, J. General Physiol. 8:115, 1925.
31. Hawkins, J. A.: A Discussion of Recent Studies on the Metabolism of Normal and Malignant Cells, J. General Physiol. 9:771, 1926; footnote 13, second reference.

and immature cells from cases of lymphatic leukemia resembled embryonic tissue.

Such comparisons are of value chiefly to bring out the fact that the metabolism of the white blood cells does differ in marked degree from that of most other normal tissues. That this difference may be of considerable physiologic importance is indicated by the work of Fleischmann,³² who showed that when cell respiration is fully inhibited by 0.005 molar hydrocyanic acid, phagocytosis and ameboid motion of leukocytes from blood as well as from peritoneal exudate are fully retained, the necessary energy being derived from glycolysis. It is suggested by Bakker and by Fleischmann that this "anoxybiotic" activity of the leukocytes may be of importance in enabling them to live and function in exudates, where the supply of oxygen is slight. Okamoto³³ has shown that malignant tissue likewise can live for several days without oxygen. While knowledge of the differences in the metabolic activity of these various types of cells is at present of chiefly theoretical interest, it is to be hoped that it may ultimately prove to be of some practical value in the understanding and treatment of disease.

SUMMARY

1. The metabolism of the white blood cells of leukemic blood varies according to the degree of maturity of the cells.

2. The oxygen consumption is greater, the more mature the cells, whereas the sugar consumption (glycolysis) tends to be smaller, the more mature the cells.

3. When calculated on the basis of weight, the rate of sugar consumption of lymphatic white blood cells does not differ from that of myelogenous cells of approximately the same degree of maturity.

4. The metabolism of normal white blood cells is similar to that of relatively mature cells from patients with leukemia, but more active, as regards both oxygen and sugar consumption.

5. Slight degrees of cell injury exert a marked effect on the rate of oxygen consumption, much less on the rate of sugar consumption.

6. When measured under aerobic and anaerobic conditions (in the presence of 95 per cent oxygen and 95 per cent nitrogen, respectively), the sugar consumption of normal white blood cells and mature myelogenous cells from leukemic blood resembles that of cancer tissue, whereas the sugar consumption of immature myelogenous cells and of both mature and immature lymphatic cells is of the type considered characteristic of embryonic tissue.

32. Fleischmann, W.: Ueber Anoxybiose von Leucocyten, *Biochem. Ztschr.* **184**:385, 1927.

33. Okamoto, Y.: Ueber anaerobiose von Tumorgewebe, *Biochem. Ztschr.* **160**:52, 1925.

II. THE DIFFUSIBLE CALCIUM AND THE PROTEINS OF THE BLOOD SERUM IN MALIGNANT DISEASES *

LEWIS GUNTHER, M.D.

LOS ANGELES

AND

DAVID M. GREENBERG, PH.D.

BERKELEY, CALIF.

WITH THE TECHNICAL ASSISTANCE OF JOHN B. DALTON

Several workers have suggested that abnormalities in calcium metabolism may be significant in the genesis and development of neoplasms in man and in other animals. Thus Clowes and Frisbie¹ found calcium to be markedly low and potassium high in actively growing malignant tissue. Goldzieher² and Theis and Benedict³ reported low values for the total serum calcium in patients afflicted with carcinoma and other malignant tumors. Reymond, Sendrail and Lassalle⁴ and Sendrail⁵ claimed that a lowering of the serum calcium occurred in the precancerous phase of animals with experimentally induced neoplasms. Finally, McDonald⁶ went so far as to state that cancer is a disease associated with a lessened amount of total and ionized calcium in the blood. These observations led us to investigate the calcium fractions, the proteins and

* Submitted for publication, Nov. 30, 1929.

* From the Department of Medicine, San Francisco, and the Division of Biochemistry, University of California Medical School, Berkeley.

* This research is one of a series carried out jointly in the Department of Medicine and the Division of Biochemistry of the University of California Medical School, with the cooperation of Professors W. J. Kerr and Carl L. A. Schmidt.

1. Clowes, G. H. A., and Frisbie, W. S.: On the Relationship Between the Rate of Growth, Age, and Potassium and Calcium Content of Mouse Tumors (Adeno-Carcinoma, Jensen), *Am. J. Physiol.* **14**:173, 1905.

2. Goldzieher, M.: Experimentelle Beiträge zur Biologie der Geschwüde, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **15**:283, 1912.

3. Theis, R. C., and Benedict, S. R.: Inorganic Constituents of the Serum in Cancer, *J. Cancer Research* **8**:499, 1924.

4. Reymond, A.; Sendrail, M., and Lassalle, C. A.: Variation of Ion Balance in Experimental Cancer, *Compt. rend. Soc. de biol.* **93**:1061, 1925.

5. Sendrail, M.: The Precancerous Phase, *Néoplasmes* **5**:99, 1926.

6. McDonald, Ellice: A Theory of Cancer Causation with Some Unfinished Results, *M. J. & Rec.* **125**:795 (June 15) 1927; abstr., *J. A. M. A.* **89**:824 (Sept. 3) 1927.

the inorganic phosphate of the blood serum in fifteen patients suffering from malignant diseases.

Recent work in the field of calcium metabolism⁷ has shown that a measurement of the diffusible fraction of the serum calcium is a measure of the physiologically available calcium as demonstrated by its decrease in tetany,⁸ and by its increase after the administration of adequate doses of parathyroid extract,⁹ or after the ingestion of calcium salts.¹⁰

By the diffusible calcium is meant that portion of the serum calcium which will diffuse through a collodion membrane completely permeable to crystalloids. Experimental work has shown that the diffusible calcium fraction of the blood serum is not entirely ionized, but that it does contain essentially the same concentration of ionic calcium as in the blood.¹¹ As opposed to the diffusible calcium, the nondiffusible calcium is that fraction of the serum calcium held back by a collodion membrane

7. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, *Physiol. Rev.* **8**:283, 1928.

8. Von Meysenbug, L., and McCann, G. F.: The Diffusible Calcium of the Blood Serum: II. Human Rickets, and Experimental Dog Tetany, *J. Biol. Chem.* **47**:541, 1921. Liu, S. H.: A Comparative Study of the Effects of Various Treatments on the Calcium and Phosphorus Metabolism in Tetany; Chronic Juvenile Tetany, *J. Clin. Investigation* **5**:259, 1928.

9. Data accumulated by the authors have not been published. Recently Cantarow (*Arch. Int. Med.* **44**:834 [Dec.] 1929), in order to avoid the theoretical drawbacks attending the direct analysis of the diffusible calcium of the serum as obtained by the combined method of ultrafiltration and diffusion, measured the spinal fluid calcium at intervals after the injection of parathormone. He assumed that the spinal fluid calcium represented at all times a measurement of the diffusible calcium of the blood. Cantarow found that the rise in the total calcium of the blood was not followed by a parallel rise in the spinal fluid and concluded thereby that it was the nondiffusible calcium fraction that increased after the injection of parathyroid hormone. His observations are in direct contradiction to those of other workers who determined the fractions of the serum calcium by direct analysis after separation through a collodion membrane. Unless it can be shown that the rate of change in the spinal fluid calcium and the magnitude of the change are identical with those in the blood stream at any given moment, while marked fluctuations are taking place in the blood stream, Cantarow's analyses of the spinal fluid must be interpreted with considerable caution in their application to the state of the diffusible calcium of the serum. In a recent communication (*J. Biol. Chem.* **85**:491 [Jan.] 1930) we discussed the theoretical objections to the direct analysis after diffusion and ultrafiltration and offered a simplified method for the direct examination of the diffusible calcium of the serum after ultrafiltration through a collodion membrane.

10. Moritz, A. R.: The State of the Serum Calcium in Experimental Hypo and Hypercalcemia, *J. Biol. Chem.* **66**:343, 1925.

11. Neuhausen, B. A., and Pincus, J. B.: A Study of Several Inorganic Constituents of Serum by Ultra Filtration, *J. Biol. Chem.* **57**:99 (Aug.) 1923. Stewart, C. P., and Percival, G. H.: Calcium in Corpuscles, Plasma and Serum, *Biochem. J.* **22**:548, 1928.

completely permeable to crystalloids. Loeb and Nichols¹² and Greenberg¹³ have shown this fraction to be bound to the proteins in the form of a calcium-protein complex ion. From this, it is to be expected that the amount of the nondiffusible calcium of the serum will depend primarily on the amount of the serum proteins present.¹⁴

Theoretically, the determination of the ionic calcium would be the ideal manner of evaluating the availability of calcium for physiologic purposes. But lacking methods of clinical practicability for such measurements, we must depend, qualitatively at least, on alterations in the diffusible calcium which contains the ionic fraction, to indicate the state of the available calcium. That this is of practical value has been demonstrated by Liu¹⁵ in chronic tetany, and by us in parathyroid tetany.¹⁶ In these diseases, in which a known deficiency in serum calcium exists, it is the decrease in the diffusible fraction of the calcium that was found to be important. If significant alterations in the functional activity of the blood calcium exist in carcinoma or in other malignant diseases, it might be expected that the values for the diffusible fraction of the blood serum calcium would show these changes.

EXPERIMENTAL WORK

The total calcium was determined by Tisdall's modification of the Kramer-Tisdall method.¹⁷ The diffusible calcium was estimated by ultrafiltration of the blood serum through a specially prepared collodion membrane, and the nondiffusible calcium was obtained by difference between the total and the diffusible calcium.¹⁴ The inorganic phosphate was determined by Fiske and Subbarow's method.¹⁸ The serum proteins were estimated according to the colorimetric method described by one of us.¹⁹ A more complete description of the experimental procedure is to be found in a communication especially devoted to this subject.¹⁴

12. Loeb, R. F., and Nichols, E. C.: Factors Influencing the Diffusibility of Calcium in Human Blood, *J. Biol. Chem.* **72**:690, 1927.

13. Greenberg, D. M.: Electrical Transference of Calcium in Blood Serum Protein Solutions, *J. Biol. Chem.* **79**:177, 1928.

14. Greenberg, D. M., and Gunther, L.: On the Determination of the Diffusible and Nondiffusible Serum Calcium, *J. Biol. Chem.* **85**:491 (Jan.) 1930.

15. Liu (footnote 8, second reference).

16. The diffusible calcium in parathyroid tetany will be the subject of another communication.

17. Tisdall, F. F.: A Note on the Kramer-Tisdall Method for the Determination of Calcium in Small Amounts of Serum, *J. Biol. Chem.* **56**:439, 1923.

18. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375, 1925.

19. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, *J. Biol. Chem.* **83**:545, 1929.

RESULTS

The analytic results are shown in the accompanying table. Seven of the fifteen patients exhibited values for the total serum calcium definitely below the normal limits in conformity with the observations of Goldzieher² and Theis and Benedict,³ which they set at from 9.3 to 10.5 mg. per hundred cubic centimeters.²⁰

Analytic Data

Patient	Calcium			Inorganic Serum Phos- phorus, Mg. per 100 Cc.	Serum Proteins in per Cent		Comment
	Total Serum, Mg. per 100 Cc.	Diffus- ible, Mg. per 100 Cc.	Nondif- fusible, Mg. per 100 Cc.		Albumin	Globulin	
Swan.....	10.5	5.2	5.3	2.6	4.0	1.6	Endothelial myeloma of humerus
Col.....	9.8	5.7	4.1	3.3	5.1	2.4	Carcinoma of lung
San* (1)...	7.6	4.8	2.8	3.6	4.0	2.6	Carcinoma of pylorus
(2)...	7.5	4.7	2.8	3.7	4.0	2.4	
(3)...	7.2	Lost	4.2	2.3	(Plasma CO ₂ = 73 per cent by volume)
Kis.....	8.1	4.0	4.1	3.1	3.6	2.8	Generalized carcinomatosis
Ysu.....	9.0	4.2	4.8	3.7	4.1	2.1	Carcinoma of sigmoid colon
Ros.....	9.3	4.4	4.9	3.7	4.4	3.6	Hemangioma of pleura
Zel.....	9.5	5.3	4.2	3.8	3.9	2.8	Hodgkin's disease
Dun.....	9.9	4.8	5.1	3.1	5.1	2.4	Carcinoma of tongue
Ash.....	9.3	4.5	4.8	3.3	4.1	2.5	Inoperable cancer of the stomach
Pat.....	9.9	4.8	5.1	3.8	4.8	2.7	Cancer of the small intestine
Fra †....	7.7	5.1	2.6	2.9	3.6	2.6	Carcinoma of ampulla of Vater
Swe †....	8.6	4.5	4.1	3.5	4.2	2.5	Carcinoma of head of pancreas
Bles †....	8.1	4.5	Primary carcinoma of cecum, secondary of liver
Mar †....	9.2	6.4	Carcinoma of head of pancreas
Bob †....	10.0	5.4	Carcinoma of common bile duct

* Sample 1 was drawn Nov. 5, 1928; sample 2, Dec. 6, 1928, and sample 3, Dec. 10, 1928.

† Patients were jaundiced. The presence of jaundice has been shown by us not to alter the diffusible calcium (footnote 16).

In marked contrast to the values for the total calcium, four being definitely below 8.5 mg. per hundred cubic centimeters, it is seen that all but one of the values for the diffusible calcium are above the lowermost limit of 4.2 mg. per hundred cubic centimeters. For the patients on whom the serum proteins were determined, it is to be noticed that there is a rough parallelism between the nondiffusible calcium fraction and the

20. In a more recent discussion, Crip and McElroy (Arch. Int. Med. 42:865 [Dec.] 1928) placed these limits for the total serum calcium between 8.5 and 11.7 mg. per hundred cubic centimeters. We have found (this issue, page 72) the normal values for the diffusible calcium of the serum of adults to vary between 4.2 and 6.8 mg. per hundred cubic centimeters and those for the nondiffusible calcium to vary between 4.1 and 7.4 mg. per hundred cubic centimeters.

content of the serum proteins.²¹ The fact that the fall of the serum proteins is concomitant with a qualitative fall in the nondiffusible calcium offers an explanation for the apparent deficiency of the blood calcium as seen in the total serum calcium values.

In six of the patients, jaundice of varying degrees was also present. We have shown in an earlier communication²² that the presence of jaundice in no way alters the conclusions to be drawn from the analytic data. The inorganic serum phosphorus in all our cases showed no significant deviations from the usually accepted normal values.

Our observations indicate that the diffusible calcium is within the limits of normal variations in malignant diseases. If the diffusible calcium may be considered a measure of the physiologically available calcium, we may conclude that it is present in adequate amounts in malignant disease, and that the blood calcium is apparently not a factor in the etiology of such diseases.

841 Pacific Mutual Building.

University of California Medical School.

21. The only striking exception to this seems to be patient San. Since we were able to run three sets of analyses on blood drawn at intervals over a period of more than a month, the analytic observations cannot be doubted. This case was also complicated by having a considerable alkalosis as shown by the plasma carbon dioxide content of 73 per cent by volume.

22. Gunther, L., and Greenberg, D. M.: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch. Int. Med.* **45**:983 (June) 1930.

III. THE DIFFUSIBLE CALCIUM OF THE BLOOD SERUM IN ALLERGIC DISEASES *

D. M. GREENBERG, PH.D.

BERKELEY, CALIF.

AND

LEWIS GUNTHER, M.D.

LOS ANGELES

The calcium metabolism in allergic diseases has recently been the subject of investigation by a number of workers. The principal method of approach has been through the study of the total calcium content of the serum by methods similar to the Kramer and Tisdall method ¹ for the analysis of the blood for calcium. Such studies have been based mostly on the assumption of a deficiency of calcium in the blood and are supported principally by the indirect evidence that symptomatic relief has been obtained in certain instances through therapy with calcium salts. The mass of the analytic data, however, critically reviewed, indicates that the total serum calcium values lie within the range of normal variation.² For a discussion of the normal values, the reader is referred to the recent work of Crip and McElroy,² who also reviewed the present status of calcium therapy in atopy.

As a part of the general problem in the study of the diffusible calcium of the blood serum in a number of pathologic conditions undertaken in this laboratory, fourteen cases of various allergic conditions were studied. Patients who were suffering from asthma of bacterial and specific protein origin, hay-fever, eczema, and urticaria caused by a specific protein and dermatographia were included.

The specimens of venous blood were for the most part obtained during fasting, in the morning. Work done in our laboratory indicates

* Submitted for publication, Nov. 30, 1929.

* From the Division of Biochemistry, Berkeley, and the Department of Medicine, San Francisco, University of California Medical School.

* This research is one of a series carried out jointly by the Division of Biochemistry and the Department of Medicine of the University of California Medical School with the cooperation of Professor William J. Kerr and Professor Carl L. A. Schmidt.

1. Kramer, B., and Tisdall, F. F.: Distribution of Sodium, Potassium, Calcium and Magnesium Between Corpuscles and Serum of Human Blood, *J. Biol. Chem.* **53**:241, 1922.

2. Crip, L. H., and McElroy, W. S.: Atopy, *Arch. Int. Med.* **42**:865 (Dec.) 1928.

that a blood specimen taken during fasting is not essential.³ The diffusible calcium was obtained by ultrafiltration of the blood serum through a collodion membrane by the method of Greenberg and Gunther.⁴ The normal concentration of the diffusible calcium of the blood serum in adults, we have found,⁵ varies in the main between 4.5 and 6 mg. per hundred cubic centimeters of serum, with extreme ranges between 4.2 and 6.8 mg. per hundred cubic centimeters and an average value of 4.96 mg. per hundred cubic centimeters. For the diffusible calcium of the blood serum of normal children, to our knowledge, no figures are as yet available.

The results are tabulated in the accompanying table. The series is not large enough for detailed statistical analysis, but indicates the general

Results of Analyses of the Blood Serum of Allergic Patients for Calcium

Patient	Age, Years	Total Calcium, Mg. per 100 Ce.	Diffusible Calcium, Mg. per 100 Ce. of Ultrafiltrate	Remarks
De*	14	9.9	4.8	Hay-fever, eczema
Ne*	11	10.2	4.4	Asthma
To*	12	9.0	4.3	Asthma, eczema, hay-fever
Ku*	9	...	4.0	Asthma
Do*	8	9.2	5.0	Asthma, hay-fever
Sh*	4.3	Asthma
Sha*	10.1	5.2	Asthma
Ne	Adult	10.3	5.3	Hay-fever, eczema
Fo	Adult	11.2	5.3	Dermatographia
Lu†	Adult	9.6	5.2	Asthma
Ku†	Adult	9.8	5.1	Asthma
Li†	Adult	10.3	5.6	Asthma
Bu†	Adult	10.1	5.2	Asthma
Ca	Adult	11.0	5.3	Dermatographia

* Blood samples were obtained through the courtesy of Dr. George Piness and Dr. Hyman Miller, Los Angeles, from their allergic service at the Children's Hospital, Hollywood, Calif.

† Blood samples were obtained through the courtesy of Dr. Albert H. Rowe, Oakland, Calif.

trend of the diffusible calcium in the allergic diseases enumerated. The analyses show that the calcium values lie within the normal range of variation, the only significant exception being the value in the case of Ku. The figures for the children's cases in the table tend to be somewhat lower than those for the adults. That the values for diffusible calcium lie within the normal range of variation in eczema, hay-fever, urticaria, etc., is a particularly significant observation, for the diffusible calcium of the

3. Unpublished data taken by the authors on experiments with the ingestion of calcium.

4. Greenberg, D. M., and Gunther, L.: On the Determination of Diffusible and Non-Diffusible Serum Calcium, *J. Biol. Chem.* **85**:491, 1930.

5. Gunther, L., and Greenberg, D. M.: I. The Diffusible Calcium and the Proteins of the Blood Serum in Jaundice, *Arch. Int. Med.* **45**:983 (June) 1930.

serum is, to all purposes, physiologically available calcium.⁶ It is this fraction of the serum calcium that contains the same concentration of ionic calcium as in the blood, although the ultrafiltrable calcium is not all ionized.⁷

Our analyses of the serum in allergic diseases show values for the diffusible and nondiffusible calcium (obtained by subtraction of the value of the diffusible calcium from that of the total calcium⁸) that vary together within the normal range; but this is so only because the diffusible calcium is normal. Data from our experiments⁹ indicate that except in diseases in which there is a marked reduction in serum proteins (which causes an abnormal degree of variation in the nondiffusible calcium), physiologic variations in the calcium occur ordinarily in the diffusible calcium fraction, often with little concomitant variation in the total calcium values. This has been shown in a striking manner in the tetany of parathyroid deficiency by ourselves,¹⁰ which also confirms the work of Liu.¹¹ In view of these facts, the observation that the total and diffusible fraction of the blood serum calcium vary together within the normal range in allergic diseases indicates that physiologically available calcium is present in the blood in adequate amounts.

841 Pacific Mutual Bldg., Los Angeles.

University of California Medical School.

6. Stewart, C. P., and Percival, G. H.: Calcium Metabolism, *Physiol. Rev.* **8**:283, 1928; Calcium in Corpuscles, Plasma and Serum, *Biochem. J.* **22**:548, 1928. Moritz, A. R.: The State of the Serum Calcium in Experimental Hypo and Hypercalcemia, *J. Biol. Chem.* **66**:343, 1925.

7. Stewart and Percival (footnote 6). Neuhausen, B. S., and Pincus, J. B.: A Study of the Condition of Several Inorganic Constituents of Serum by Means of Ultrafiltration, *J. Biol. Chem.* **57**:99 (Aug.) 1923.

8. Greenberg and Gunther (footnotes 4 and 5).

9. Gunther and Greenberg (footnote 5); II. Studies on the Diffusible Calcium and the Proteins of the Blood Serum in Carcinoma and Other Malignant Diseases, this issue, p. 67.

10. The tetany of parathyroid deficiency will be the subject of another communication.

11. Liu, S. H.: A Comparative Study of the Effects of Various Treatments on the Calcium and Phosphorus Metabolism in Tetany; Chronic Juvenile Tetany, *J. Clin. Investigation* **5**:259, 1928.

SO-CALLED MALIGNANT HYPERTENSION

A CLINICAL AND MORPHOLOGIC STUDY *

FRANCIS D. MURPHY, M.D.

AND

JOHN GRILL, M.D.

MILWAUKEE

Recent work in America and abroad has emphasized the importance of a group of rapidly fatal cases associated with excessive hypertension. Among the various terms that have been employed to define this condition those most commonly used are "malignant hypertension," "malignant renal sclerosis of Fahr," "genuine contracted kidney" and "chronic interstitial nephritis."

The term "malignant hypertension" was first used by Volhard and Fahr¹ to designate cases of renal arteriosclerosis in which renal failure later developed. They assumed that the condition was caused by the addition of an inflammatory process to a kidney already damaged by arteriosclerosis, leading to infarction and necrosis of the glomerular loops. Fahr² later introduced the anatomic expression "malignant renal sclerosis" to designate changes in the kidney characterized by necrosis of the afferent glomerular arterioles and the capillary loops, with inflammatory changes in the corresponding glomerulus.

Keith, Wagener and Kernohan³ employed the term "malignant hypertension" in a slightly different sense. They applied it to a clinical condition with the following characteristics: persistent hypertension with a progressively downward course, moderate or no renal failure, absence of anemia, cardiac hypertrophy and distinctive changes in the retina. Anatomically, they emphasized the widespread involvement of the arterioles of the entire body.

Since there has been considerable difference of opinion concerning the essential nature of this class of cases, the present investigation was undertaken in an attempt to contribute to the correlation of the clinical observations and the corresponding morphologic changes in the arterial

* Submitted for publication, Dec. 3, 1929.

* From the Medical Clinic and Laboratories of the Milwaukee County Hospital and the Department of Medicine, Marquette University.

1. Volhard, F., and Fahr, T.: *Die Brightsche Nierenkrankheit*, Klinik Pathologie und Atlas, Berlin, Julius Springer, 1914.

2. Fahr, T.: *Ueber Nephrosclerose*, Virchows Arch. f. path. Anat. **226**:119, 1919.

3. Keith, Norman M.; Wagener, Henry P., and Kernohan, James W.: *The Syndrome of Malignant Hypertension*, Arch. Int. Med. **41**:141 (Feb.) 1928.

Summary of Clinical Data

Case	Age, Years	Date	Renal Function Tests										Urinalysis			Chief Complaint	Duration of Illness Prior to This Study
			Blood Chemistry			Phthal- cin, per Cent		Concentration		Urea Con- centration	Albu- min	Doubly Refract- ing Li- poids	Micro- scopic Observa- tions				
			Sys- tolic	Diastolic	Non- protein Nitro- gen	Creat- inine	Choles- terol	Hours	Highest Specific Gravity					Lowest Specific Gravity			
1	34	2/18/23	210	115	44	2.4	178	35	1.018	1.005	..	0	0	Negative	Red Blood Cells	4 years	
	34	4/13/23	180	100	38	1.8	...	40	1.020	1.006	..	0	0	Negative		
	34	7/17/23	240	160	104	4.2	160	10	1.009	1.004	15	+++	0	Many red blood cells; few white blood cells; no casts	2,050,000	Headache and abdominal cramps	
2	42	8/22/23	255	160	55	1.4	255	40	1.018	1.008	38	0	0	Negative	4,040,000	Headache and loss of weight	
	42	1/30/20	200	170	49	2.0	178	25	1.023	1.010	30	0	0	Negative	Headache and dyspnea	
3	37	3/23/24	215	125	38	1.5	...	75	1.024	1.004	..	0	...	Negative	5,400,000	Dizziness and loss of strength	
	41	6/ 3/23	230	150	34	1.9	...	60	1.025	1.010	..	++	...	Few red blood cells; pus cells and casts	4,000,000	Headache; loss of weight and strength	
	41	3/12/23	200	160	51	2.2	166	30	1.015	1.009	..	+++	...	Many red blood cells; pus cells and granular casts	3,140,000		
4	57	12/ 2/20	240	150	52	2.9	104	10	1.010	1.006	20	+	0	Few red blood cells and granu- lar casts	3,310,000	Headache and loss of weight	
	57	1/ 4/27	220	150	70	2.8	109	15	1.015	1.005	..	++	0	Few red blood cells and granu- lar casts	Headache and loss of weight	
5	53	11/ 7/26	210	115	48	3.2	150	25	1.008	1.004	..	+++	0	Many red blood cells and gran- ular casts	4,500,000	Headache, dyspnea and weakness	
		1/15/27	245	150	120	8.0	142	5	1.011	1.007	..	+++	0	Many red blood cells and gran- ular casts	Headache and emaciation	
6	52	7/29/25	230	125	42	...	154	15	1.020	1.005	60	+++	0	Few red blood cells; pus cells and casts	4,000,000	Headache	
7	53	11/16/26	180	110	36	...	210	15	45	+	0	Headache	
	52	12/21/26	205	130	40	2.0	265	70	1.024	1.010	52	++	0	Negative	4,080,000	Headache and left-sided paralysis	

system of the body. For the purpose of this study, sixteen cases were selected from a total of 629 cases studied between Jan. 1, 1925 and July 1, 1929. This total group included all cases in which the diagnosis was chronic nephritis, arteriosclerosis with hypertension or essential hypertension. Cases of decrescent or senile arteriosclerosis were omitted from the study. Of the sixteen patients, thirteen died; on twelve, autopsy was done. In the clinical study, attention was directed especially to the hypertension and renal function, the condition of the heart and the larger peripheral arteries, and cerebral and retinal changes. Histologically, smaller arteries and arterioles were especially studied in the kidney, liver, pancreas, spleen, heart and skeletal muscle; we were rarely permitted to examine the brain.

ANALYSIS OF THE CLINICAL DATA

There was a wide variation in the clinical manifestations of the patients, depending on the development of heart failure, renal failure, cerebral hemorrhage and the rate of progress of the disease. Six patients died of renal failure, three of heart failure, two of apoplexy and one of a ruptured dissecting aneurysm on the basis of an atherosclerotic ulcer in the aorta. Some patients, for example the one in case 2, developed both renal failure and heart failure toward the close of the illness.

The ages of the patients in this series ranged from 9 to 57 years. Eight patients were above 40 and eight were under 40 years of age. Three were above 50, while three were less than 19 years of age. The sex and age of the patients appeared to have no influence on the severity of the symptoms and the rapid progress of the disease. A systolic blood pressure of 250 or above and a diastolic pressure of 150 or above were not unusual observations. The interval that elapsed between the onset of hypertension and the occurrence of symptoms referable to hypertension was not known in all cases, although in case 2 it was at least eight years. In other cases an interval of from two to five years was known to have elapsed. It is known that in case 3 the blood pressure was normal eight months before the onset of symptoms. Aside from the height of the blood pressure, it was observed that the hypertension of this group did not show the fluctuation seen in the early stages of the so-called "benign" group. Blood pressure reducing substances brought about a fall in pressure in cases 8 and 9, but there was no alleviation of the chief symptoms. On discontinuing the treatment, the blood pressure promptly rose to its former high level. In no case was there a definite remission in the hypertension as is often seen in the early benign form, but the hypertension persisted from the onset until the end.

Renal function was carefully studied in all the cases reported here. The laboratory data in connection with tests of kidney function are given in the table. Renal failure with uremia developed in six cases. Convulsive seizures occurred only in case 2. Albuminuria was present in all the cases during the later periods of the disease. It was difficult to determine accurately in most instances just how long albuminuria had existed before the last illness, although in most cases it is certain that albuminuria developed late in the disease. Undoubtedly there was considerable variability in the period of time elapsing between the onset of the hypertension and the onset of albuminuria. In some patients albuminuria developed early in the course, and in others later on, probably depending on the severity of changes in the vessels of the kidney. A striking feature of the urinary picture was hemorrhage from the kidneys in cases 1 and 8. In case 1 the hemorrhage could be accounted for at autopsy from the necrosis of the arterioles and glomerular loops, but in case 8 no necrotic areas were found.

Palpation of the peripheral arteries, such as the radials, temporals and brachials, disclosed no constant gross changes. It was found that in general the patients above 40 years of age had tortuous arteries the walls of which were hardened, and that those under 40 had wiry, straight arteries which were under tension but the walls of which could not be called hardened. Some arteries were calcified, such as those described in case 5. No doubt there are numerous other factors, not under consideration here, which contributed to the tortuosity and thickness of the peripheral arteries.

With regard to the condition of the heart in the cases studied, there were wide variations. Cardiac hypertrophy was present in every case, although more pronounced in some than in others. Despite the great increase in the size of the heart in some of the patients, circulation was unimpaired and death came through other channels. Heart failure caused death in three of the cases. Pulmonary edema and profound dyspnea, usually worse at night (cardiac asthma), were the chief clinical manifestations. In most cases, the liver was enlarged and firm; in the cases of heart failure, it was engorged and tender. Cyanosis and Cheyne-Stokes' respiration, with moderate edema and ascites, were clinical features of patients who died of heart failure.

The Wassermann reaction of the blood was positive, four plus, in two cases; in case 8 it was negative, although both the father and the mother had syphilis. It does not appear, then, that syphilis is an essential factor in exciting malignant hypertension.

Abdominal cramps simulating gallstone colic were frequently present, though not constantly so, in cases 1 and 8. Definite anemia was found in eight of the sixteen cases studied; it was moderate in all these cases except 1 and 8 in which it was severe. In the early periods

of the disease, anemia was usually not present, but developed in the later stages and especially in those cases characterized by renal failure. An outstanding symptom in all cases was headache; it was the first symptom complained of in most cases, and often made life almost unbearable for the sufferer. These symptoms in conjunction with the ophthalmoscopic observations in some cases suggested a diagnosis of tumor of the brain. Marked weakness and loss of weight were present in all cases; frequently these developed to a pronounced degree before signs of renal failure, heart failure or cerebral hemorrhage occurred.

From the ophthalmologic standpoint, all cases showed either a choked disk or retinal edema accompanied by hemorrhages. The arteries were narrowed, and in some cases straight, in others tortuous. The retinal changes were indicative of various degrees of neuroretinitis. Hemorrhages from the nose, the stomach and the intestinal tract were found in case 8. Nausea and vomiting were present in all cases.

The clinical features in the cases described here differed from those in essential or benign hypertension. The chief dissimilarity consisted in the greater severity of symptoms and the rapid functional breakdown of the involved organs in the malignant type. That there should be variation in the clinical observations is expected from the nature of the disease. Essentially, the malignant type is a widespread disorder of the arterial system of the body, involving many or all bodily structures and leading at times to a more profound impairment of one organ than of another. Furthermore, some organs and structures of the body may be severely affected by this vascular disease without any functional disturbance being felt by the patient. This is exemplified by the extensive vascular changes seen in the spleen in all cases. In most of the cases presented here, the hypertension syndrome existing prior to the onset of the last illness had the qualities of a benign hypertension. The forces responsible for the conversion of the benign into the malignant form are not known.

ANALYSIS OF PATHOLOGIC DATA

All sections were studied with hematoxylin and eosin, van Gieson's and Weigert's elastic tissue stains and sudan III. Polariscopic examinations were done when fat was found. The outside diameter of many of the smallest arteries and arterioles was measured with a micrometer. The smallest arteries and arterioles were found to measure from 40 to 120 microns. Postmortem examinations were made in cases 1 to 12 inclusive. There was considerable dissimilarity in the morphologic changes in the organs and blood vessels, both grossly and microscopically. The heart was always found to be hypertrophied and there usually was arteriosclerosis of the larger branches of the coronaries. The walls of the smaller branches were thin and appeared fairly normal.

The size and the appearance of the kidneys were decidedly variable. Some kidneys were small, granular and contracted; others were larger than normal and smooth, and resembled those in subacute glomerular nephritis. In case 1, the kidneys had the appearance of those in embolic focal glomerular nephritis. Some kidneys were whitish and others were reddish. On microscopic examination, the smallest arteries and arterioles of the kidney as well as of the spleen, pancreas, liver and brain were almost universally involved in an arteriosclerotic process. The diffuse intimal thickening, causing a narrowing of the lumina, was characterized in some cases more by hyperplastic elastic thickening with proliferation of intimal connective tissue, and in others more by fatty and hyaline degeneration. Both processes were often combined in the same kidney. A striking feature was the hypertrophy of the media in some of the arterioles and smallest arteries of the kidney and other organs. In cases 2, 3, 4, 8, 9 and 11, in which these medial changes were distinct and conspicuous, there were also arteriosclerotic changes either of the same vessel or of some vessel in an adjoining area. Although many of the smallest arteries and arterioles in these cases showed hypertrophy of the media, the arteriosclerotic changes with reduction of the media were the outstanding features. In cases 5 and 7, although no medial hypertrophy was found in the renal vessels, it was present in the arterioles of the liver and spleen. In cases 1 to 7 inclusive, there were necrotic lesions in the walls of the afferent arterioles and many capillary loops in the corresponding glomeruli. The changes in these seven cases corresponded to the descriptions of malignant renal sclerosis of Fahr. In many tufts there was an increase of the endothelial cells of the capillary loops with a cellular exudate; in a few, epithelial crescents were found in Bowman's capsular space. Occasionally areas of lymphocytic infiltration and fibrosis were observed, replacing the renal functional tissue. The adventitia of the smallest arteries and arterioles was often found to be thickened. Periarterial lymphocytic infiltration was present in the interstitial connective tissue surrounding some of the smallest arteries and arterioles. Usually the adventitia did not participate in this reaction. In case 3, erythrocytes were seen to be infiltrating the necrosed arteriolar wall. In addition to the more acute and destructive lesions, an advanced arteriosclerotic process was seen, involving the smallest arteries and arterioles of the kidney.

The changes in the kidneys in cases 8 to 12 inclusive consisted of advanced arteriosclerosis of the smallest arteries and arterioles, leading in places to partial or complete obliteration of the lumina. No necrotic lesions were found in the glomerular loops. Some of the glomeruli showed fibrosis and hyalinization. Aside from the necrotic changes seen in the kidney in cases 1 to 7, the microscopic lesions in all cases

were essentially arteriosclerotic. None of the cases studied presented the histologic evidence characteristic of chronic glomerulonephritis. The smallest arteries and arterioles of the skeletal muscles of the body were studied in eight of the sixteen cases reported. In cases 2, 3, 8, 9, 10, 12 and 14, the media was found to be definitely thickened and there were no evidences of arteriosclerotic changes such as were found in the other organs of the body. No changes were found in case 11. No examination was made in the other cases. The smallest arteries and arterioles of the lungs appeared to be normal in all cases except one (case 9) in which there was hypertrophy of the media. Although advanced arteriosclerotic processes were seen in the vessels of the pancreas, spleen and liver, paralleling in severity those of the kidneys, no necrotic changes were found outside of the kidney. The microscopic changes in the vessels of the organs studied appeared to be manifestations of various degrees of an arteriosclerotic process.

Briefly, the changes in the smallest arteries and arterioles may be summarized as follows:

1. The lumina were almost universally narrowed and were sometimes obliterated by thickening of the vessel walls.
2. Hyperplastic elastic thickening of the intima was found, with proliferation of the connective tissue of the intima.
3. Fatty and hyaline degeneration involving the intima, and frequently the media, was prominent.
4. Medial thickening, consisting of hypertrophy of the muscular tissue, frequently occurred alone or in association with degenerative lesions of the intima.
5. Degenerative and proliferative lesions in the intima were usually accompanied by medial atrophy.
6. Occasionally there was periarterial lymphocytic infiltration of the interstitial connective tissue surrounding the smallest arteries and arterioles of the kidney.
7. Necrotic lesions were present in the walls of the arterioles and in the loops of the corresponding glomeruli in six cases.
8. Combinations of these changes were at times found involving the same vessel; in other cases the various lesions could be demonstrated side by side in the same histologic specimen.
9. The vessels of the skeletal muscles frequently showed thickening of the media, with normal intimal tissue.
10. The smallest arteries and arterioles of the lung were normal in all but one case.

COMMENT

Following the pioneer work of George Johnson⁴ and of Gull and Sutton,⁵ profound interest was aroused in a class of cases in which

4. Johnson, George: *Lectures on Bright's Disease: With Especial Reference to Pathology, Diagnosis, and Treatment*, London, 1873.

5. Gull, William; and Sutton, Henry: *On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney (Arterio-Capillary Fibrosis)*, *Tr. Medico-Chir. Soc. London* 55:273, 1872.

there were clinical hypertension, cardiac hypertrophy and termination with uremia, heart failure or apoplexy. Morphologically, a granular contracted kidney was found so commonly that the disease came to be called by names expressing the renal features. Of the many terms, those chiefly used were "red granular kidney," "contracted granular kidney" and "genuine Schrumphniere."

Although the lesions of the kidney were singled out for careful study, Gull and Sutton⁵ suggested that many organs were diseased in this morbid condition and that the minute arteries in the kidney, spleen, brain, retina and skin were involved. It was also emphasized that the clinical picture might vary according to the structures chiefly affected, and that several or all organs might be affected simultaneously.

It was the opinion of George Johnson⁴ that not only were the minute arteries in the kidney thickened, but the minute arteries of the skin and other parts of the body were similarly changed; and he attributed the thickening to hypertrophy of their muscular tissue. He maintained that the kidneys were primarily at fault and incapable of secreting noxious agents, with the result that there developed a constriction of the arterioles of the body and subsequently a rise in the blood pressure and hypertrophy of the musculature of the smaller arteries and arterioles. Gull and Sutton believed differently, claiming that the vascular changes were independent of renal disease, and that the chief alterations consisted of a "hyaline-fibroid" formation, chiefly in the adventitia and intima, with atrophy of the muscular layer. They introduced the term "arteriocardillary fibrosis" for these changes.

Jores⁶ who worked on the same problem with better methods, described the intimal thickening. He discovered that the intimal changes consisted of hyaline and fatty degeneration and elastic hyperplastic thickening of the intima. Such changes, according to Jores, led to narrowing of the lumen of the smaller arteries and arterioles. Jores failed to confirm Johnson's observation of medial muscle hypertrophy, and he agreed with Gull and Sutton that the vascular changes were widespread, leading at times to kidney disease and at other times to brain or heart failure with normal renal function. Jores found extensive degenerative changes in the intima of the arterioles of the brain, spleen, liver, pancreas and gastro-intestinal tract. In speaking of the media of the arteries and arterioles, he denied the existence of muscular thickening. He found the media reduced, and he emphasized again that the entire process was one of arteriosclerosis.

An examination of the case reports of the older writers shows conclusively that they encountered the class of cases described in recent

6. Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch. f. path. Anat.* **178**:367, 1904.

years as malignant hypertension, although they did not attempt to differentiate the various types of vascular sclerosis. Gaskell,⁷ however, separated the large class of primary vascular diseases into two groups. In the first subgroup he placed those characterized by a slow alteration of the kidney which was produced by what he called senile arteriosclerosis. In the second subgroup he found that the chief changes were due to a pronounced involvement of the arterioles and smallest arteries, and that they were distinguished clinically from the first class by a very high blood pressure, renal failure, cardiac hypertrophy and their occurrence in younger persons. Evans,⁸ in describing the lesions of the smaller arteries and arterioles in diffuse hyperplastic sclerosis, stated that medial hypertrophy is a common observation, but that it is not the essential element nor a constant feature. The main feature in his opinion is an intimal thickening. The medial hypertrophy, he said, may be attributed to the hypertension.

The descriptive adjectives "benign" and "malignant," which were introduced by Volhard and Fahr,¹ aimed at separating renal arteriosclerosis into two distinct groups. The benign form included those cases in which the arteriosclerosis of the kidneys was not accompanied by renal insufficiency, while the malignant form included those in which there were inflammatory changes in the glomeruli and afferent arterioles in addition to the arteriosclerosis. This was the "combination form" or "bösaartig" hypertension. Both authors later discarded the term "combination form." Volhard⁹ introduced the theory that ischemia of the arterioles, dependent in part on vasoconstriction and in part on the swelling of the arteriolar walls, was the determining factor in the production of malignant hypertension.

According to Fahr,¹⁰ the clinical differentiation between benign and malignant hypertension is readily accepted; but a unanimity of opinion concerning the pathogenesis of the two forms is difficult to obtain. Fahr expressed his belief that one is justified in speaking of two forms and not of two stages of renal sclerosis. He differentiated between the benign form and the malignant form of renal sclerosis. In the benign form, there is simple arteriosclerosis of the larger arteries and arterioles. There are fatty and hyaline degenerative changes in the afferent arterioles, with obliteration of many glomeruli. The tubules are normal, and

7. Gaskell, J. F.: On the Changes in the Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidney Disease, *J. Path. & Bact.* **16**:287, 1912.

8. Evans, Geoffrey: On the Nature of Arteriosclerosis, *Brit. M. J.* **1**:454, 1923.

9. Volhard, Franz: Die doppelseitigen hämatogenen Nierenerkrankungen (Bright'sche Krankheit), Berlin, Julius Springer, 1919, vol. 8, p. 576.

10. Fahr, T.: Ueber die Beziehungen von Arteriolenklerose, Hypertonie und Herzhypertrophie, *Virchows Arch. f. path. Anat.* **239**:41, 1922.

there is an increase of the interstitial connective tissue. Inflammation and necrotic changes are absent. Fahr compared this benign form with the arteriosclerotic contracted kidney described by Ziegler,¹¹ a condition affecting elderly people and distinguished histologically by arteriosclerosis of the larger and smaller arteries without renal failure. The malignant renal sclerosis of Fahr is distinguished from the benign form by the presence of inflammatory and necrotic changes in the arterioles and the glomeruli. In the tubular regions there are areas of round cell infiltration. Fahr expressed the opinion that malignant sclerosis may be a process restricted to the arterioles, but that at times larger arteries are involved. Extensive hyperplastic elastic intimal thickening of interlobular arteries may be present. A profound fatty and hyaline degeneration of the intima of the arterioles is found, with narrowing and occlusion of the lumen. In places there is extensive fatty degeneration of the entire arteriolar wall. Necrosis of the arteriolar wall is found, with infiltration by red blood cells. The glomeruli may be obliterated, partly collapsed or infarcted; other tufts may appear normal. There are cases in which the necrotic changes in the glomerular loops resemble embolic focal glomerular nephritis. In the larger renal arteries there is thickening of the media, with proliferative and degenerative changes in the intima.

That Fahr¹² found difficulty in separating sharply the benign from the malignant form is seen from his reports in which he described borderline cases or decompensated benign sclerosis. In this group there was no necrosis of the arterioles and glomerular loops, but there was a pronounced narrowing of the arterioles produced by arteriosclerosis, leading to a break-down of renal function.

Concerning the cause of malignant sclerosis, Fahr expressed the belief that vascular poisons affect the arterioles; some are unknown and some known. He assumed that the virus of rheumatic fever may at times be responsible for it. In his opinion, syphilis is an important factor in the pathogenesis of malignant sclerosis. The benign form of arteriosclerosis is due to wear and tear in a large sense. With respect to the involvement of the arterioles of the skin and skeletal muscles in malignant sclerosis, Fahr described various changes. Occasionally a mild arteriosclerotic process is found, with atrophy of the media. Usually he found these vessels normal. Sometimes the media is well developed in the arterioles and smaller arteries of the skin, the skeletal muscles and the intestinal tract. He stated that it is hard to decide

11. Ziegler, E.: Ueber die Ursachen der Nierenschrumpfung, *Deutsches Arch. f. klin. Med.* **25**:586, 1880.

12. Fahr, T.: Kurze Beiträge zur Frage der Nephrosklerose, *Deutsches Arch. f. klin. Med.* **134**:366, 1920.

whether an actual hypertrophy of the media exists because of the difficulty in judging the thickness of the wall. Fahr concluded that the arteriosclerotic changes are not caused by hypertension but that there are other forces causing the arteriosclerosis.

Arteriolonecrosis of the kidney was the term applied by Herxheimer¹³ to a condition resembling Fahr's malignant sclerosis. He disagreed with Fahr's distinction between benign and malignant sclerosis, and maintained that they are terms applied to different stages of the same process and not to separate diseases. Herxheimer described cases of renal arteriosclerosis with uremia in which no changes corresponding to the malignant sclerosis of Fahr were found. Herxheimer attributed the chief lesions to rapidly developing arteriosclerotic changes in the arterioles in some cases, but he believed that these are the result only of the arteriolar sclerosis and not of an added inflammatory process. Many glomeruli have widened and ruptured loops, leading to hemorrhage into Bowman's capsular space. Grossly and microscopically, he stated, these kidney may resemble those of embolic focal glomerular nephritis seen in endocarditis, lenta. Herxheimer described these arteriosclerotic lesions not only in the kidney but also in the liver, spleen, pancreas and brain, while he found other arterioles of the body free from changes.

Löhlein,¹⁴ after investigating the arteriosclerotic contracted kidney, disagreed with Fahr that benign and malignant sclerosis were different in nature. He agreed with Jores, who also had studied this problem, and he concluded that there was no added inflammatory factor. It was emphasized by Löhlein that there was a difference in the size of the artery involved and in the extent of the arteriosclerotic process. In the benign form he found the arteries involved, with little glomerular disease, while in the malignant form the arterioles were universally diseased and glomeruli correspondingly involved. The arteriosclerotic process, however, was identical in both cases, but in the malignant form there were advanced degenerative and proliferative changes which weakened the arteriolar wall in places, leading to dilatation. When such arteriosclerotic processes were severe enough, necrosis of the arteriolar and glomerular loops was present, and a histologic picture almost identical with glomerular nephritis was seen. Löhlein¹⁵ did

13. Herxheimer, G.: Ueber Arteriolonekrose der Nieren, *Virchows Arch. f. path. Anat.* **251**:709, 1924.

14. Löhlein, M.: Ueber Schrumpfnieren, *Beitr. z. allg. Path. u. path. Anat.* **63**:570, 1917.

15. Löhlein, M., quoted by Kaufmann, E.: *Pathology*, Philadelphia, P. Blakiston's Son & Company, 1929.

not consider these changes indicative of an added inflammatory process. He summarized the glomerular changes as follows:

Necrobiosis after collapse of all or portions of the loops subsequent to occlusion; then degeneration and atrophy with appearance of scars and remnants and débris of the Malpighian bodies; this is followed on the one hand, by reactive proliferative phenomena, degenerations, lipoid infiltration and cellular invasion, and on the other, by more or less retained structures in the loops. The changes remind us of chronic glomerulonephritis and are easily mistaken for inflammation.

Löhlein considered the glomerular changes similar to those in the arterioles; he stated that it was the tissue destruction which stimulated the reactive inflammatory processes, and that for this reason the latter were reparatory.

Löhlein found degenerative changes in the media of the larger arteries and arterioles of the kidney, but he did not mention that he found hypertrophy. He stressed the fact that in the malignant form the arteriolar lumen was narrowed in contrast to the benign form in which the lumen was wider than normal. The hypertension cannot be explained on the basis of arteriosclerosis, according to Löhlein.¹⁶ The sclerosis is the effect of hypertension.

Hypertrophic changes in the media of all vascular structures of the body are described by Hueck¹⁷ in his studies on arteriosclerosis. The elastic hyperplastic thickening of the intima, like medial hypertrophy of the arteries, is not classed as arteriosclerotic by Hueck but is an adaptation or functional phenomenon. Degenerative changes may follow these processes of adaptation, but not necessarily.

In his description of the "true arteriosclerotic contracted kidney," Kaufmann¹⁸ mentioned a "second form," which developed suddenly, leading quickly to renal insufficiency, apoplexy or profuse hemorrhage. Anemia was a feature in contrast to the robust appearance of persons suffering from the usual form. The "second form" corresponds to malignant hypertension. Kaufmann expressed his belief that Fahr's benign and malignant types are only differences in degree of an arteriosclerotic process. He found no changes in the vessels of the body musculature.

In 420 cases of primary hypertension, Bell and Clawson¹⁹ found thirty-six with definite renal insufficiency; twenty-seven of the thirty-

16. Löhlein, M.: *Zur Nephrocirrhosis arteriosclerotica*, *Med. Klin.* **14**:136, 1918.

17. Hueck, Werner: *Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose*, *München. med. Wchnschr.* **67**:535, 573 and 606, 1920.

18. Kaufmann, E.: *Pathology*, Philadelphia, P. Blakiston's Son & Company, 1929.

19. Bell, E. T., and Clawson, G. J.: *Primary (Essential) Hypertension: A Study of Four Hundred and Twenty Cases*, *Arch. Path.* **5**:939 (June) 1928.

six cases had a slowly progressive form of renal insufficiency ending eventually in uremia. Histologic examination of the kidneys in this group revealed a profound narrowing of the smaller arteries and arterioles, leading to a pure ischemic atrophy of the glomerular apparatus. Nine cases were characterized by uremia which came on rapidly. Histologically, necrosis of the arteries and arterioles was found, often with infarcted glomeruli. In four of the nine cases, acute inflammatory changes were seen in a few glomeruli. Aside from these inflammatory changes, the process may be interpreted as severe acute arteriosclerosis, according to Bell and Clawson. The term "malignant," they stated, may be properly applied to the nine cases of hypertension with acute uremia, but it is ill adapted to describe all cases of hypertension with uremia. They failed to find any definite changes in the skeletal muscles and the skin.

It is clear that the majority of the investigative work in this class of vascular disease has been directed at the kidney. Undoubtedly this results from the facts that the kidneys are always the seat of profound changes and that changes in the kidney are more likely to excite functional disturbances than changes in other organs. For it is evident that a severe arteriosclerosis may develop in an organ such as the spleen without any functional deficiencies being felt by the patient, while the same changes in the kidney would lead to advanced renal failure.

Keith, Wagener and Kernohan³ were the first in this country to emphasize and clearly define the clinical features of malignant hypertension. They described the typical retinal changes occurring in patients with excessive hypertension, and the rapid downward course in conjunction with the functional failure, not of one organ, but of several organs simultaneously. They pointed out that the malignant hypertension may occur in young persons, or may be superimposed on a previous general arteriosclerosis or benign hypertension. It was found that the chief disturbances were in the retina, brain, heart and kidney. Typical symptoms of renal failure and of disease of the coronaries were infrequently found in their series. Of their eighty-one patients, seventy-four died within fifty-one months, and the majority within two years. Autopsies were done in seven cases. Microscopically, the most outstanding features were the diffuseness of the lesions and the degree of involvement of the smaller arteries and arterioles, while the larger arteries and capillaries were free from changes. All organs and tissues, even the arterioles of the skeletal muscles, were severely involved. In every case the kidneys showed profound changes. The walls of the smaller arteries and arterioles were thickened and the lumina were narrowed. The thickening, the writers stated, was due to hyperplasia of the intima with hypertrophy and splitting up of the intimal elastic lamina, as seen in arteriosclerosis. In addition, they found hypertrophy

of the muscular tissue of the media as well as an increase of fibrous tissue of the adventitia in all their cases. In no case did they find necrotic changes in the arterioles. In places the arteriole lumen was obliterated, due to the intimal hyperplasia and hypertrophy of the media. The almost total absence of signs of degeneration in the intimal layer of the smaller arteries and arterioles led them to believe that this process was distinct from simple arteriosclerosis. In a later report, Anderson, Kernohan and Keith²⁰ described an intermediate group, composed of cases of the severe benign or early malignant type. The cardiac, retinal and renal functions were remarkably good; the peripheral arterioles showed involvement equal to that in the malignant group.

In our series of cases we were able to confirm in general the clinical observations described by Keith and his associates under the term "malignant hypertension." Typical retinitis, a persistent excessive hypertension and a simultaneous functional break-down of more than one vital organ were prominent features. Headache and rapid loss of strength and weight were the two striking symptoms. Keith and his co-workers observed that anemia was absent in their series of cases; we were unable to confirm this, as anemia was practically always present in our cases, especially in the later stages of the disease. Renal failure was a more conspicuous observation in our series than in those described by Keith, Wagener and Kernohan; this difference may be ascribed to the fact that more of our cases were seen in terminal stages. The clinical differentiation between chronic glomerular nephritis with renal failure, and malignant hypertension with renal failure may be difficult unless one knows what has gone on before the patient comes under observation, although when renal failure develops in the course of malignant hypertension the downward progress is much more rapid than in chronic glomerular nephritis. Furthermore, definite remissions are likely to occur in the course of chronic nephritis, while in malignant hypertension there are no remissions; progress downward is so rapid that it appears justifiable to call this the most malignant of all renal diseases.

Histologically, our observations correspond essentially with those of Keith and his associates. We found numerous types of histologic changes in the smallest arteries and arterioles of the kidneys, pancreas, spleen and liver. Frequently larger arteries of the organs participated in the same process. Although a variety of lesions were seen, even in the same microscopic section, the general features were those of arteriosclerosis. Occasionally, the walls of one of the smallest arteries or

20. Anderson, E. W.; Kernohan, J. W., and Keith, N. W.: Histologic Studies of the Peripheral Arterioles in Ambulatory Patients with High Blood Pressure, *Proc. Staff Meetings Mayo Clinic* 3:314, 1928.

arterioles were found almost completely transformed into homogeneous mass consisting of hyaline and fatty changes, while an adjacent vessel in the same microscopic area showed hyperplastic elastic thickening of the intima with connective tissue proliferation. Often but not constantly these processes were found combined in the same vessel. At times the media and adventitia of the smallest arteries and arterioles were found to be thickened, but such changes existed in conjunction with arteriosclerosis of the same vessel or of those adjacent to it. Medial hypertrophy was less conspicuous when the arteriosclerotic process was an advanced one. In some cases necrosis was present in the walls of the afferent glomerular arteriole and of the loops of the corresponding glomeruli. When present, the necrosis appeared to be a part of an already existing severe arteriosclerosis. In some cases the necrotic changes were widespread and numerous, and in others they were few and scattered. In cases in which the necrotic process is extensive, the changes excited in the glomeruli and surrounding tissues resemble those of inflammation. Fahr¹¹ claimed that this is an added inflammatory process; Herxheimer,¹³ Jores²¹ and Löhlein¹⁴ expressed their belief that it is a severe degree of arteriosclerosis. Severe arteriosclerotic changes may be found in cases of chronic glomerular nephritis, as has been pointed out by Fishberg.²² This fact may occasionally lead to difficulty in interpretation of the histologic changes.

With respect to the changes in the media of the arterioles of the skeletal muscle, various degrees of thickening were found. Frequently the change consisted of a medial thickening leading to a pronounced narrowing of the lumen; occasionally no definite change was found, and at times it was difficult to state whether a thickening existed or not.

Clinically, it appears that malignant hypertension is a later phase of benign hypertension, differing from the benign form in the greater severity of its symptoms, the more rapid functional break-down of the essential organs of the body and the more persistent and more excessive hypertension. Some patients who have had benign hypertension for years may, for unknown reasons, develop the malignant form.

The assumption that malignant hypertension is characterized by a generalized vascular disturbance affecting the smallest arteries and arterioles of the entire body appears to be correct. It is seen in case 7 that cerebral hemorrhage terminated the course of the disease and that on examination of the kidney profound changes, including a few

21. Jores, L.: Ueber den pathologischen Umbau von Organen, *Virchows Arch. f. path. Anat.* **221**:14, 1916.

22. Fishberg, A. M.: The Arteriolar Lesions of Glomerulo-Nephritis, *Arch. Int. Med.* **40**:80 (July) 1927.

areas of necrosis, were found. One may assume that had the cerebral accident been postponed for a time, renal necrosis might have progressed far enough to produce renal insufficiency.

Morphologically, the lesions of malignant and benign hypertension are of the same general pattern. The striking changes in both forms are arteriosclerotic. The arteriosclerotic process of the malignant type not only affects the larger and smaller arteries, but involves the smallest arteries and the arterioles of almost the entire body. In the malignant form the lesions appear to be progressing more rapidly, producing a greater narrowing of the lumina and leading to more profound functional disturbances in the essential organs of the body. The hypertrophy of the musculature of the arterioles may be changes of adaptation due to strain imposed by hypertension. The chief difference between the benign and the malignant form of hypertension appears to be one of degree.

CONCLUSIONS

1. Sixteen cases of malignant hypertension are analyzed. Of the sixteen patients, thirteen died and on twelve autopsy was done.

2. Clinically, the chief observations were headache, a profound loss of weight, a persistent excessive hypertension, functional failure of one or more essential organs, a progressively downward course and a rapid termination. A characteristic retinopathy was present in all cases.

3. Histologically, the essential lesions were arteriosclerotic. The smallest arteries and arterioles were almost universally involved. In six cases necrotic lesions had developed in the walls of the afferent glomerular arterioles and in the loops of the corresponding glomeruli. Hypertrophy of the media of the arterioles of the skeletal muscles was usually found. In the arterioles of the kidneys and other organs, medial hypertrophy was found occasionally, in association with arteriosclerotic changes.

4. The clinical and morphologic observations on malignant hypertension differ from those on hypertension of benign form only in degree. Greater severity of the clinical symptoms and a more extensive and destructive form of lesion of the smallest arteries and arterioles are characteristic of malignant hypertension.

REPORT OF CASES

CASE 1.—H. L., a white bartender, aged 34, was first observed by us in February, 1928. His chief complaint was headache and loss of weight. In March, 1924, he began to lose weight and strength; on examination the only positive observation was hypertension of 210 systolic, 115 diastolic. During the following four years the blood pressure varied from 180 systolic, 110 diastolic to 220 systolic, 130 diastolic. In the early summer of 1928, he became worse. Headache, visual disturbances and cramps developed, and he entered this hospital on July 10.

The blood pressure was 250 systolic, 135 diastolic. The radials were tense and wiry, and the vessel walls were thicker than normal. Renal function was definitely impaired. No cardiac enlargement was found. No murmurs were heard. The abdomen appeared normal, although the abdominal cramps were more troublesome than the severe headaches. Ophthalmoscopic examination revealed: bilateral choked disks, more severe in the right eye than in the left; fresh hemorrhages throughout both retinas; atrophic changes more pronounced in the right eye than in the left. The Wassermann reaction of the blood was negative. The disease made rapid progress, and renal function steadily declined. The headaches and the cramps became worse. On July 25, uremia without convulsions set in, and the patient died on July 26.

Observations at autopsy were: Both kidneys were larger than normal, and the surfaces were smooth; the right one weighed 175 Gm., and the left 170 Gm. Over the surface of both kidneys were many petechial hemorrhages, giving the appearance of the "flea-bitten" kidney. On section, considerable blood was seen in the pelvis of both kidneys; large petechial hemorrhages were numerous throughout the pelvic mucous membrane. The markings were well defined, and the pallor of the cortex and columns of Bertini stood out in sharp relief against the darker medullary portion. A moderate thickening of the walls characterized the renal arteries and their larger branches. Microscopically, many glomeruli appeared normal; others had the appearance of an embolic focal glomerulonephritis. Some of the glomerular loops had undergone necrotic changes, while other loops appeared normal. There was a cellular exudate in Bowman's capsular space, and definite epithelial-like crescents were found in places. Examination of the arterioles revealed a necrosis of the wall of the afferent glomerular arterioles, corresponding to the necrotic glomeruli. Not all the arterioles showed necrosis. In some there was profound intimal thickening produced by fatty degeneration, connective tissue proliferation or hyaline change, leading to partial occlusion of the lumen in some places and to complete occlusion in others. In some areas the media shared in the degenerative changes found in the intima. Although the media of smaller arteries and arterioles occasionally seemed thicker than normal, this was found to be the effect of an extension of a fatty degeneration of this layer. Frequently an end-arteritis of the smaller arteries was found, with a fatty degeneration of the media. Throughout the smaller arteries the elastic tissue was proliferated. In the interstitial connective tissue surrounding some of the smallest arteries and arterioles there was perivascular leukocytic infiltration. The thickened adventitia was found to be free from these changes. In the tubules there was slight fatty degeneration of many epithelial cells. This fat did not doubly refract polarized light. In the cortex there were definite areas of leukocytic infiltration. Intimal thickening was present in the smaller arteries and arterioles of the liver, causing almost complete obliteration of the lumen in places. Fatty and hyaline degeneration predominated, with atrophy of the media. In some places the intimal degenerative changes were mild, and here the media appeared thickened. The same type of degenerative changes were found in the spleen as in the liver, except that they appeared to be more severe; no necrosis of the walls was found in the spleen.

CASE 2.—J. L., a white laborer, aged 42, entered the hospital on Aug. 22, 1928, complaining of severe headache, dizziness, weakness and palpitation of the heart. He had been in the hospital in June, 1920, and had had a herniotomy done under local anesthesia; blood pressure at that time was 220 systolic and 120 diastolic, and the urine, heart and renal function were apparently normal. At that time the patient had no complaint referable to the hypertension. On reentrance to the hospital, his blood pressure was 255 systolic and 160 diastolic. The radial and

temporal arteries were wiry and tortuous. Renal function was normal. Ophthalmoscopic examination revealed areas of old organized infiltrates in the fundi; many yellowish white spots and recent hemorrhages were seen in the macular areas. The Wassermann reaction of the blood was negative. The headaches and weakness became worse. The patient lost weight rapidly; from an average of 215 pounds (97.5 Kg.), his weight had diminished to 160 pounds (72.5 Kg.) on his entrance to the hospital, and he weighed about 128 pounds (58 Kg.) at death, which occurred on Feb. 3, 1929, from bronchopneumonia and heart failure.

Autopsy revealed that the heart was large and weighed 655 Gm. The wall of the left ventricle measured 33 mm. The aortic leaflet of the mitral valve contained an atherosclerotic patch. Pronounced atherosclerosis was found in the aorta. The coronaries had lumina of normal size. Both kidneys were smaller than normal; the right one weighed 117 Gm., and the left 134 Gm. They were granular. On section, the cortex was found to be thinned; there were many hemorrhagic areas in the pelvic mucosa, and considerable blood was found in the pelvis. The renal arteries were thickened and arteriosclerotic. Microscopic examination showed that many glomeruli were intact; the loops were normally filled with blood. Other glomeruli had undergone fibrosis, hyalinization or atrophy. A few showed distinct necrosis of some of the loops, and the afferent arteriole revealed the same necrotic changes. Most of the arterioles and the smallest arteries had degenerative and proliferative changes in the intima, with atrophy of the media. Fatty degeneration extended from the intima into the media in some places. Endarteritic lesions were numerous, occasionally leading to obliteration of the lumina. In some areas the media of the arteriolar wall was profoundly thickened and the intima appeared to be intact. The adventitia was found to be universally thickened. The lumina of the arterioles were narrowed throughout and frequently occluded. There was fatty degeneration of the epithelial cells of the convoluted tubules, and some of the fat doubly refracted polarized light. There was an increase of the interstitial tissue of the kidney. Sections from the pectoralis major and diaphragm showed many arterioles to be occluded; the intima was normal. Extensive hypertrophy of the media was found. The vessels of the lungs were normal. No changes were seen in the arterioles of the brain. The media of the smallest arteries was normal.

CASE 3.—M. D., a white woman, aged 41, was first observed in 1920, when a breast was amputated for a tumor, which proved to be benign. At that time the blood pressure was 160 systolic, 110 diastolic, and the heart and kidneys were normal. She came under observation again in March, 1924, because of weakness, headache and dizziness. The blood pressure was 215 systolic and 120 diastolic. Arteriosclerosis of the retinal arteries was found, but no edema or hemorrhages were seen. The radial arteries were thickened. The heart was enlarged; the urine was normal, as was the nitrogen content of the blood. In June, 1928, the patient reentered the hospital complaining of pain in the back of the neck, referred over the back of the head. She had lost 40 pounds (18.1 Kg.) and was very weak. Nocturia, albuminuria, palpitation of the heart and vomiting had set in. At first the renal function was good, but it began to fail gradually. Aside from enlargement, the heart was normal. There was no edema. Ophthalmoscopic examination revealed hemorrhagic areas in both fundi, and moderate edema of both retinas. The Wassermann reaction of the blood was negative. During the following four months, the symptoms became exaggerated, and vomiting became pronounced. The patient died in true uremic coma on October 4.

At autopsy, both kidneys appeared reduced in size and coarsely granular. The right kidney weighed 110 Gm., and the left 132 Gm. On section, the peripelvic fat was seen to be increased. In the cortex, and especially at the corticomedullary boundary zone, the arteries stood out prominently. The renal artery and its main branches were abnormally thickened, so that the lumina were reduced in size. Microscopically, numerous glomeruli appeared normal; others were hypertrophied, and many had undergone complete hyalinization or necrosis. Fatty degeneration was found in some of the partially obliterated tufts. There was profound thickening of the walls of the smallest arteries and arterioles. In places the entire wall was hyalinized, and occasionally necrosis was found. This necrotic process extended into the hilus of the glomerulus, leading to necrosis of the corresponding loops of the glomerulus. Erythrocytes were seen to infiltrate the walls of a few necrosed arterioles. Periarterial leukocytic infiltration was present in the adventitia and in the interstitial connective tissue surrounding some of these vessels. Some arterioles were characterized by fatty degeneration of the entire wall. Throughout the kidney the lumina of the smallest arteries and arterioles were narrowed, almost obliterated in areas. The thickening of the walls was chiefly due to intimal degenerative changes. Frequently, the intimal changes extended into and involved the media. There was a definite increase in the elastic tissue throughout the vessels. In no arteriole of the kidney could hypertrophy of the media be made out. In the liver, the lumina of the smallest arteries were narrowed as a consequence of the thickening of the vessel wall. The intima was almost universally thickened because of fatty and hyaline degeneration and proliferation of connective and elastic tissue. In most areas the media was thinned, while in some places the media and the adventitia were definitely thicker than normal. In the epithelial cells of the tubules there was considerable fatty degeneration; none of the fat was doubly refracting. An increase of interstitial fibrous tissue was present and there were areas of cellular infiltration. In the pancreas, the intima of the smaller blood vessels was thickened. In some vessels there was thickening of the media and adventitia, although some of the smaller arteries showed degenerative changes in the media. Fibrous tissue proliferation, fatty degeneration and hyalinization were present in the same vessel wall. In some of the smallest arteries of the spleen, fatty degeneration of the intima and thickening of the media with widening of the lumina was found; in others, with the same degree of fatty degeneration, the media was thicker than normal, with narrowed lumina. Some of the smallest arteries showed no intimal changes, but there were hypertrophic and proliferative changes in the media and adventitia. The elastic tissue was universally hyperplastic. The arterioles and smallest arteries of the lungs were normal. In the pectoralis major muscle the media was hypertrophic in places, although some of the arterioles appeared normal.

CASE 4.—A. K., a white laborer, aged 57, entered the hospital on Dec. 2, 1926, complaining of headache, dyspnea and weakness for the previous year. The symptoms had gradually become worse until one month prior to entrance, when the headache and weakness became so severe that he was confined to bed. His weight, which normally was 160 pounds (72.5 Kg.), gradually diminished; on his admission to the hospital it was 100 pounds (45.3 Kg.). The blood pressure was 240 systolic and 150 diastolic. The radial vessels were tortuous, thickened and wiry. Renal function was greatly reduced. Aside from a moderate enlargement, the heart was normal. Ophthalmoscopic examination showed a moderate retinal edema of both fundi, with numerous hemorrhagic areas. The Wassermann reaction of the blood was four plus. On Jan. 14, 1927, he became weak, developed pulmonary edema and died of uremia.

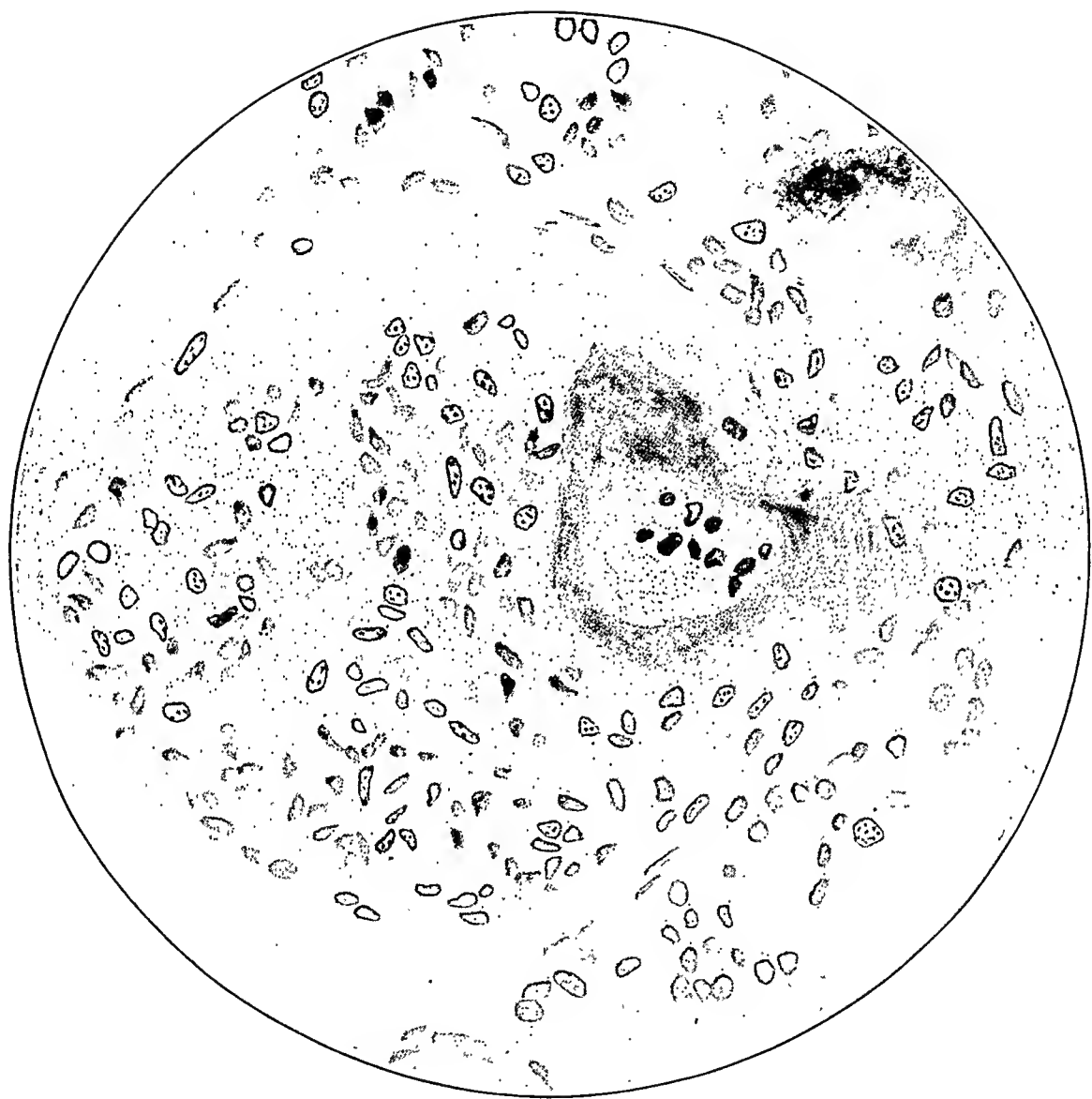


Fig. 1 (case 1).—A glomerulus showing necrosis of the afferent arteriole with extension into the glomerular loops. Hematoxylin and eosin stain; $\times 500$.

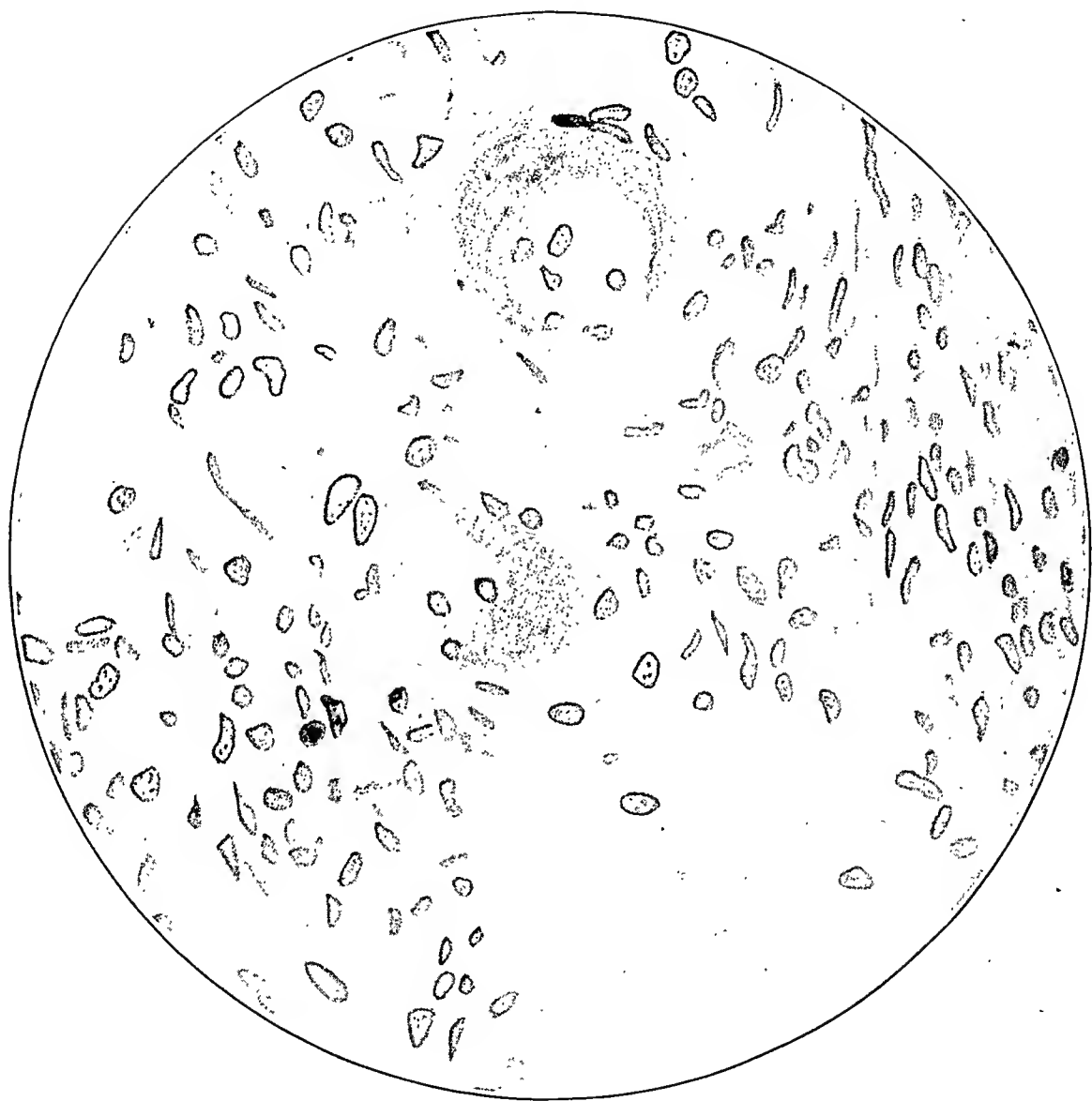


Fig. 2 (case 2).—Arterioles from the kidney, illustrating necrosis of the walls. Hematoxylin and eosin stain; $\times 500$.

At autopsy the heart weighed 500 Gm.; the valves were normal. Both kidneys were greatly contracted. The right kidney weighed 41 Gm., and the left 64 Gm. They were coarsely granular. On section, the peripelvic fat was found to be increased. The cortex was thinned, and the markings were obscured. Microscopic examination showed widespread fibrosis of the glomeruli. In places the glomerular capsule was thickened with fibrous tissue. The loops in some areas

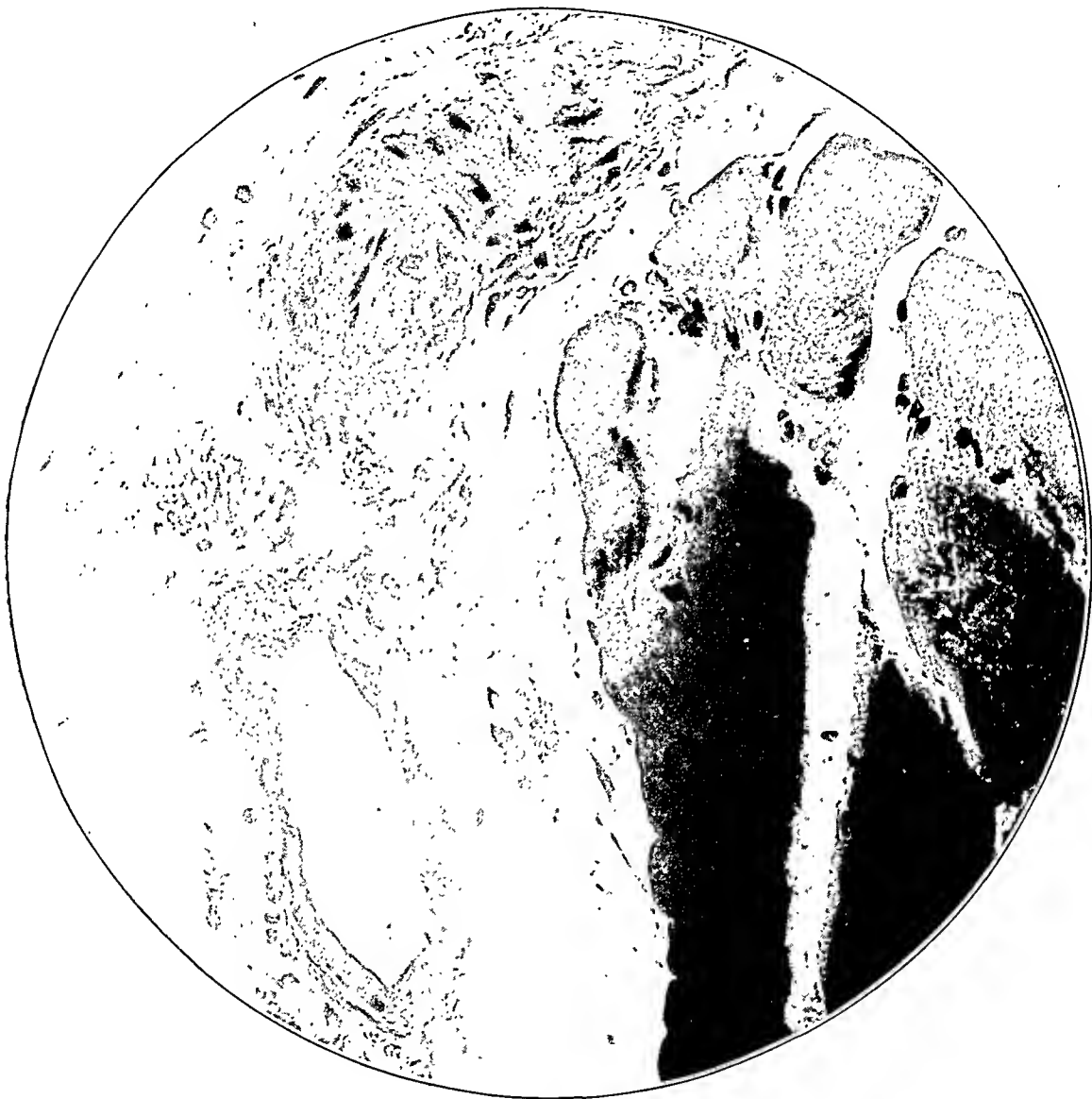


Fig. 3 (case 2).—An arteriole from the pectoralis major muscle showing hypertrophy of the media and narrow lumen. Hematoxylin and eosin stain; \times 450.

contained blood. The arterioles were universally narrowed, due to thickening of the arteriolar wall. This thickening was produced chiefly by connective tissue proliferation of the intima. Occasionally, hyaline or fatty degeneration was seen in the intima. Elastic tissue hyperplasia was pronounced throughout the arterial tree. A moderate thickening of the media of many arterioles was seen. In the walls of numerous afferent arterioles there was a necrotic process extending into

smaller vessels were universally narrowed. Hypertrophy of the media in the arterioles was seldom found. Elastic tissue was increased. The larger arteries of the kidney were arteriosclerotic. In the larger arteries, including the renal, decided arteriosclerosis had occurred, with medial atrophy. Many tubules had become completely replaced by connective tissue; the epithelium lining the convoluted tubules had undergone cloudy swelling, but little fatty degeneration was found. An extensive increase of the interstitial connective tissue had occurred. Definite arteriosclerosis with narrowed lumina and medial atrophy characterized arteries of all sizes in the liver. Similar changes were present in the spleen and the pancreas.

CASE 7.—C. D., a white man, aged 32, entered the hospital on Dec. 9, 1926, because of a slight cerebral hemorrhage. In 1918 he was denied admission to the U. S. Army on account of hypertension. At that time he was told that his blood pressure was 200. According to the history, subsequent examinations revealed no albuminuria or any other defect except the hypertension, which persisted around 200. On entrance to the hospital his blood pressure was 205 systolic and 130 diastolic. The radials were small and cordlike, and the walls were thicker than normal. Renal function was good. Aside from enlargement to the left, the heart was normal. Ophthalmoscopic examination showed many retinal hemorrhages with moderate papilledema in the retina. The Wassermann reaction of the blood was negative. On May 31, 1927, there was another cerebral hemorrhage which caused death.

Autopsy revealed that the heart was enlarged and weighed 585 Gm. Left ventricular hypertrophy was pronounced. No disease of the valves was found. Profound atherosclerosis was present in the aorta and in the coronaries, but there was no coronary occlusion. Both kidneys were smaller than normal and coarsely granular in appearance; the right kidney weighed 132 Gm., and the left 118 Gm. The walls of the main renal arteries were thickened with an atherosclerotic process. On section, the cortex appeared to be thinned and the markings were obscured. Microscopic examination showed that the glomeruli in general were well preserved. Frequently, fibrosed and atrophic tufts were found adjacent to a normal glomerulus. A striking feature was the finding of necrosed loops in some glomeruli; in addition to the necrosis of the loops, cellular exudation and the formation of epithelial crescents had occurred. The smallest arteries and arterioles were universally diseased. Many of them were occluded because of the thickened vessel wall. The chief changes were hyaline and fatty degeneration of the intima, which frequently involved the media. In places there were endarteritic changes, with fatty degeneration of the media. There were areas of arteriolar necrosis; other areas showed complete obliteration of the arterioles, associated with hyaline and fatty changes that appeared to be progressing toward necrosis. The adventitia was thickened throughout. No medial hypertrophy was found. There was cicatrization of the interstitial tissue. The tubular epithelial cells had undergone cloudy swelling and fatty degeneration, but the fat did not doubly refract polarized light. The vessels of the lungs were normal. The extensive arteriosclerotic process found in the kidney was present also in the arteries and arterioles of the liver. There was no necrosis of the vessels of the liver. Occasionally, hypertrophy of the media was found in a small artery and arteriole. There was a well developed arteriosclerotic process in the spleen similar to that seen in the kidney.

CASE 8.—L. P., a white school girl, aged 17, began to complain of headache and vomiting in July, 1927. These symptoms progressively became worse until November, 1927, when she developed a profound visual disturbance. An oculist

found choked disks and retinal hemorrhages and he suspected tumor of the brain. On Nov. 30, 1927, the blood pressure was 270 systolic and 155 diastolic. The radial and temporal arteries were cordlike and hard to compress. There was no renal insufficiency. No cardiac enlargement was found and the heart was normal. Urinalysis revealed bloody urine; later the condition entirely cleared up. Ophthalmoscopic examination showed bilateral choked disks, with many petechial hemorrhages in the periphery of the retina; the veins were full, and the arteries thin and straight. The headache and vomiting became worse. By March, 1928, the patient had lost 25 pounds (11.3 Kg.). Severe epigastric pain developed and recurred periodically; morphine was necessary for relief. The Wassermann reaction of the blood was negative on several occasions; the father died of syphilis and the mother gave a four plus Wassermann reaction. Renal apoplexy developed in May, 1928. Hematemesis occurred during the final week of illness. The patient died in true uremia on June 2. The heart showed slight hypertrophy of the left ventricle, but there were no defects of the valves. The right kidney was smaller than normal, weighing 95 Gm. It had a coarsely granular surface. The renal artery was thickened, and on cut section the smaller arteries stood out prominently. In the pelvis there was considerable old blood, and in the mucosa many recent petechial hemorrhages were seen. The cortex was thickened and the corticomedullary markings were obscured. Histologic examination showed the glomeruli to be well preserved; some were sclerosed, while others had undergone hyaline or fatty degenerative changes. Occasionally a glomerulus was seen in which some of the loops were converted into a granular and cellular mass without erythrocytes. The arterioles were universally diseased. The lumina were universally narrowed and in some places completely occluded. The changes in the arterioles for the most part were in the intima which was thickened; the media was occasionally found to be thickened. Adventitial thickening was universally present. Fatty degeneration of the intima of the arterioles was widespread, frequently extending into and involving the media. The connective tissue was increased in the adventitia and in the intima. In the smaller arteries the elastic tissue was hyperplastic. In no place were there necrotic changes in the arterioles or in the glomeruli. In some areas there was advanced fatty degeneration of the cells lining the convoluted tubules; many tubules were atrophied and were undergoing replacement by connective tissue. In the pectoralis major muscle, the media of the small arteries and arterioles was profoundly thickened, almost occluding the lumen in some areas; the intima was intact. The outstanding change in the liver was a general hypertrophy of the media of the arterioles; the intima was generally intact. In the spleen the arteriolar wall was found to be completely hyalinized in places; in other places it was thickened, due to medial hypertrophy. The intima was normal in most areas. The smallest arteries and arterioles of the lung were normal.

CASE 9.—D. D., a white girl, aged 10, entered the hospital on Sept. 3, 1927, complaining of persistent headache, dizziness and insomnia for the previous year. The following data were abstracted from the records of over two years' study in the hospital and in the outpatient clinic: The blood pressure was 205 systolic and 155 diastolic on admission to the hospital. Several convulsive seizures developed immediately prior to entrance. The radials were cordlike and thickened. Renal function remained unimpaired. There was a pronounced enlargement of the heart to the left, and a systolic mitral murmur was heard. On ophthalmoscopic examination of the right eye, the disk appeared normal in size and color; the arteries were very thin and not tortuous. Many hemorrhages were seen to follow the course of the arteries. The same condition was seen in the left eye, except that

the loops of the glomerulus. In the interstitial tissue surrounding these necrosed vessels there were areas of lymphocytic infiltration. Exudative and proliferative changes were found in the tuft. Fatty degeneration of the epithelial cells of the convoluted tubules was present. The interstitial tissue was increased. Examination of the liver showed portal cirrhosis. There was an advanced arteriosclerosis, involving the smaller and smallest arteries and arterioles of the liver. Occasion-

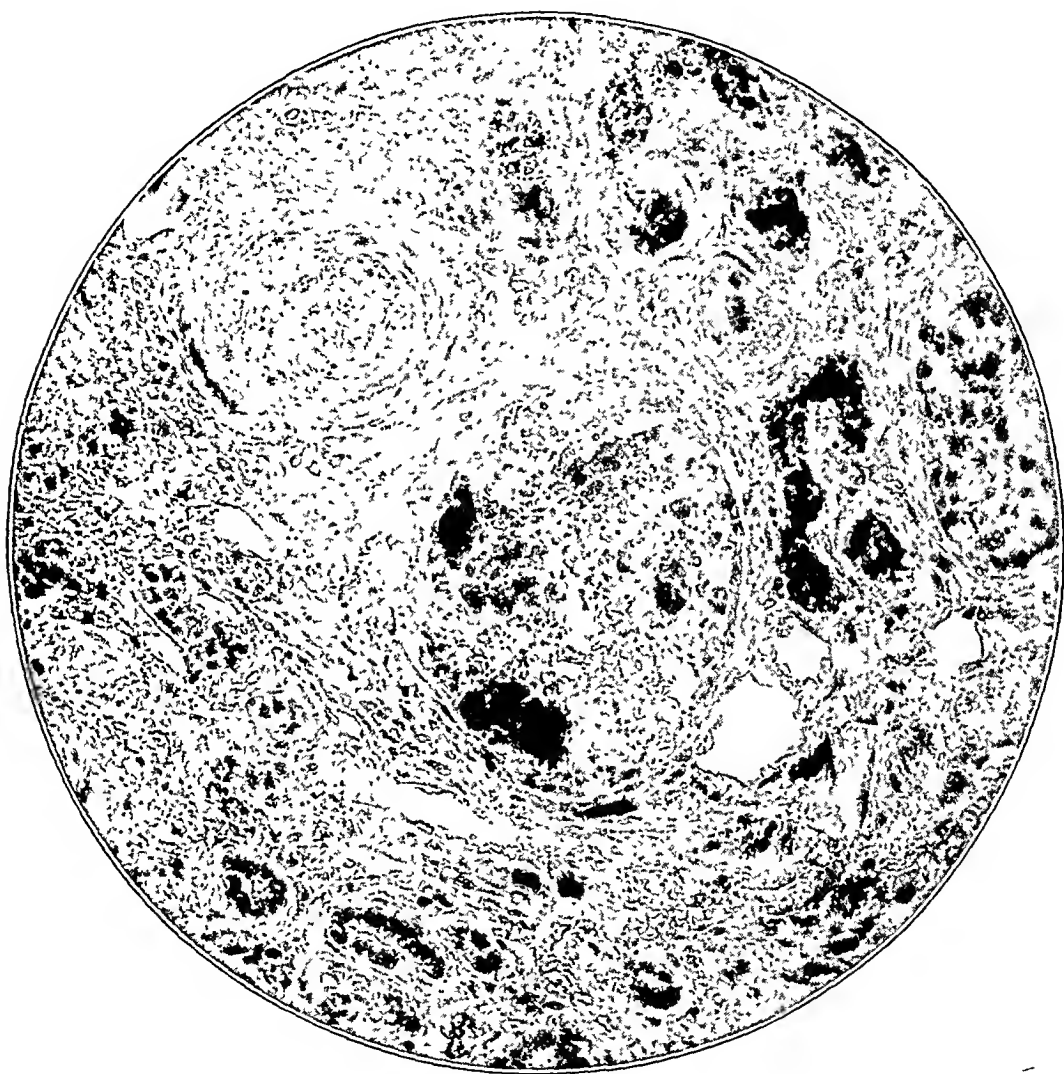


Fig. 4 (case 3).—A small artery and a glomerulus. The lumen of the small artery is obliterated and the necrotic wall is infiltrated with red blood cells. The glomerulus shows areas of necrosis.

ally there was medial hypertrophy. The vascular changes in the spleen resembled those in the liver. The smallest arteries and arterioles of the lung were normal.

CASE 5.—M. B., a white laborer, aged 53, was admitted to the hospital on Nov. 7, 1926, complaining of headache, dyspnea and loss of weight for the previous three months. The blood pressure was 190 systolic and 120 diastolic. The radial and temporal arteries were tortuous and of the pipe-stem variety. Renal function was greatly reduced. Aside from a pronounced enlargement to the left and a

systolic aortic murmur, the heart was normal. Ophthalmoscopic examination revealed that the veins were full and the arteries tortuous and thinned; considerable edema around both disks and numerous hemorrhagic areas along the course of the arteries were found. The Wassermann reaction of the blood was four plus. The weakness, loss of weight, and headache became worse. Renal function rapidly failed, and a true uremia developed with some twitching but no convulsions. The patient died on Jan. 25, 1927.

At autopsy the heart was enlarged, weighing 480 Gm. The left ventricle was twice as thick as normal. There were no defects of the valves, except atherosclerosis of the aortic cusps, which was a part of the extensive atherosclerosis of the aorta. Both kidneys were contracted and granular; the right weighed 65 Gm., and the left 70 Gm. The walls of the larger arteries were thickened and the lumina were narrowed throughout. On section, the pelvic areas were filled with fat. Microscopic examination showed that many glomeruli were fibrosed or hyalinized. In some of them there were remnants of old epithelial crescents. Many glomeruli appeared normal. Numerous loops of many glomeruli were undergoing necrosis; necrotic changes were found in the afferent arterioles corresponding to the loops. In many arterioles the intima was the seat of fatty degeneration; but the outstanding change was proliferation of the intimal connective tissue. The arteriosclerotic process caused narrowing of the lumina in places, and in other areas the lumina were completely obstructed by endarteritis obliterans. In no place could medial hypertrophy be seen; medial atrophy was universal. Interstitial connective tissue was increased, and a plasma cell infiltration, with fixed tissue proliferation, was found. There was fatty degeneration of the epithelium of the convoluted tubules. This fat did not doubly refract polarized light. In the spleen there was an increase in the connective tissue. Pronounced arteriosclerosis was seen; there was complete hyalinization of the walls of many arterioles, with occlusion of the lumina. Fatty degeneration was present. The liver, arteries and arterioles also were arteriosclerotic. Medial hypertrophy was seen in arterioles of the liver and the spleen.

CASE 6.—R. M., a white man, aged 52, was admitted to the hospital on July 26, 1925, complaining chiefly of headache, dyspnea and palpitation of the heart. Until the onset of the present trouble, he had always been well. His blood pressure was 230 systolic and 100 diastolic. The radial arteries were thickened. Renal function was reduced. The heart was enlarged to the left, and there was an apical systolic murmur transmitted to the axilla. Ophthalmoscopic examination showed an increase in the light reflex of the arteries, with moderate retinal edema; hemorrhages, old and recent, were present. The Wassermann reaction of the blood was negative. On Dec. 16, 1926, the patient died of apoplexy.

Autopsy revealed that the heart weighed 565 Gm. Left ventricular hypertrophy was marked. The valves were normal. Both kidneys were decidedly contracted and coarsely granular; the right one weighed 94 Gm., and the left 102 Gm. The peripelvic fat was increased. In places the demarcation between cortex and medulla could not be seen; the cortex was remarkably thinned. Microscopically, extensive glomerular atrophy was found; many glomeruli were fibrosed, others hyalinized. A few glomeruli had necrotic loops corresponding to necrosis of the afferent glomerular arterioles. Proliferation of Bowman's capsule and an increase in cellular elements were outstanding features. A few epithelial crescents were present. The smaller arteries and arterioles were characterized by connective tissue proliferation in the intima. In a few, fatty degeneration of the intima was found. Occasionally, there was necrosis of the arteriolar wall. The

the macular area was free from change. The Wassermann reaction of the blood was negative. Under treatment, during the two years of observation, the blood pressure came down to as low as 130 systolic and 70 diastolic. On April 4, 1928, there was a sudden rise in blood pressure to 260 systolic, 150 diastolic. Renal apoplexy developed on October 16, and the blood pressure was 228 systolic and 170 diastolic. Anemia was present at times in the course of the disease. Heart failure slowly developed, which caused death on May 27, 1929. The heart was enlarged and weighed 315 Gm. The left ventricular wall measured 1 cm. Both kidneys were contracted and granular; the right weighed 75 Gm., and the left 25 Gm. Microscopic examination showed the loops of many glomeruli to be well filled with blood. Occasionally a glomerulus was found with an exudate in Bowman's capsular space, with thickening of the capsule. No necrotic loops were seen, and many glomeruli had undergone atrophy. Practically all the arterioles were narrowed and many obliterated. The chief change was an intimal connective proliferation, although fatty degeneration of the intima was occasionally seen. The elastic tissue of the smallest arteries had undergone hyperplasia. Frequently the endothelial cells of the intima were increased. In some vessels such changes would be present in an otherwise normal vessel, and in others a degeneration of the media and intima were found. The media of the arterioles and the smallest arteries varied in appearance; in some the media was thicker and in others decidedly thinner than normal. The epithelium of the tubules was universally swollen and undergoing granular degeneration. Fatty degeneration was extensive around the central veins of the liver. A distinct hypertrophy of the media of the smallest arteries and arterioles was seen, which practically occluded the lumina in places. Slight intimal degeneration was found. The arteries and arterioles of the spleen were profoundly diseased. In most of them the lumen was reduced to a considerable degree; in others complete occlusion had occurred. The thickening of the walls was confined almost entirely to the intima which was occupied by hyaline substance. The entire vessel wall was occasionally converted into a homogeneous mass. Some of the arteriolar walls were degenerated with fat deposits. In a few arterioles the fat did not border the lumen, but appeared between the media and the proliferated intimal tissue. Some of the smaller arteries of the pancreas showed medial hypertrophy; otherwise, the changes resembled those found in the liver. Sections from the pectoralis major showed the adventitia and media so extensively thickened that the lumen was almost obliterated; the intima appeared normal. In the lungs the walls of many of the arterioles were thickened, due to hypertrophy of the media. In places the lumina were almost occluded.

CASE 10.—G. H., a colored woman, aged 56, was admitted to the hospital on Nov. 8, 1928, complaining of vomiting, dyspnea and exhaustion. According to her daughter, the patient had had high blood pressure for the previous five years. The urine, she said, had been free from albumin until the present "break-down," which occurred early in October, 1928. The blood pressure was 235 systolic and 120 diastolic. The radials were thickened, tortuous and full. Renal function was definitely impaired. Extensive hypertrophy of the heart was found. Generalized transient edema was present. Ophthalmoscopic examination showed the disks and media to be hazy; the macular area had atrophic and fresh choroidal exudate with pigment. The veins were full, and the arteries thin and tortuous. Numerous hemorrhages were visible in both retinas. The Wassermann reaction of the blood was negative. On June 4, 1929, the patient died of heart failure.

At autopsy, the heart was eccentrically hypertrophied to the left, and weighed 480 Gm. Aside from a moderate thickening of the mitral valve, no defect was found. Both kidneys were contracted and granular; the right one weighed 29

Gm., and the left 70 Gm. On cut surface, the cortex was very thin and the markings practically obliterated. Many small hemorrhages were found in the pelvic mucosa. The largest and smallest arteries were prominent and their lumina were decidedly narrowed. Microscopically, many glomeruli appeared normal; some were congested. In places Bowman's capsules were thickened from an increase in connective tissue, causing the glomerular loops to appear as if clothed in a shell of connective tissue. There were areas of leukocytic infiltration in the cortex. No areas of necrosis were found in the glomerular loops. Many of the smallest arteries and arterioles were occluded by thickening of the intima. The intimal thickening consisted of fatty degeneration; in others, there was no fatty degeneration but proliferation of connective tissue was seen, with elastic tissue hyperplasia. Frequently these intimal changes occurred together, and in places the media as well as the intima was involved. Despite the universal and profound degenerative changes present there were no arteriolonecroses. Hypertrophy of the media was not seen. Fatty degenerative changes were found in the convoluted tubules; many tubules had become replaced by fibrous tissue. A pronounced endarteritis obliterans was present in some arterioles of the liver. No medial hypertrophy was seen. Arteriosclerosis of the type described for the kidney was the striking feature of both the liver and spleen. Sections from pectoralis major and diaphragm showed that the media was hypertrophied, the lumina greatly narrowed and the intima normal. The larger arteries of the body were uniformly thickened. The chief changes consisted of hyperplasia of the connective and elastic tissues of the intima, with increase of the adventitial tissue. The media appeared normal.

CASE 11.—L. C., a white housewife, aged 42, entered the hospital on Dec. 27, 1928, complaining of headache and pains in the back, arms, legs and chest for the previous eight months. She had entered the hospital on April 4, 1927, and had undergone an operation. The records showed that the blood pressure at that time was 190 systolic and 100 diastolic; the urine was normal. The blood pressure on last admittance was 230 systolic and 115 diastolic. The radials were wiry and hard to compress. Renal function was moderately reduced. Cardiac enlargement was pronounced. No edema was present. Ophthalmoscopic examination showed a choked disk in the left eye; the arteries were thin and tortuous. The vessels were pinched off in the disk, and pulsations were observed in the superior vessels. The right eye was about the same as the left except for some hemorrhagic areas. The Wassermann reaction of the blood was negative. There was a rapid loss of strength and weight, and the headaches and pains became more pronounced. On Jan. 11, 1929, a convulsion set in and the patient died that night. At autopsy the heart appeared very large, weighing 612 Gm.; the valves were intact. Pronounced atherosclerosis was present in the aorta and coronaries; there was no coronary occlusion. The left kidney was cystic and weighed 19.5 Gm.; the right one weighed 137.5 Gm., and had a finely granular surface. On section, the cortex was found to be thinned, the peripelvic fat increased and the corticomedullary markings obscured. The striking feature was the prominence of the arteries through the cut surface; it could be seen with the naked eye that the arteries were almost obstructed from the thickened walls. On microscopic examination, many glomeruli appeared normal; the capillary loops were filled with blood. Others were atrophic and hyalinized. Fatty degeneration of Bowman's capsule was seen in the degenerating tufts. Numerous arterioles were occluded by intimal thickening produced by fatty and hyaline degeneration. The endothelial cells of the intima were proliferated in places, and behind this there was fatty or at times hyaline degeneration extending back into the media. In some of the smallest arteries there was hyper-

trophy of the media, existing alone, or in association with degenerative and proliferative changes in the intima. The elastic tissue was increased in the arteries, showing splitting of the internal elastic lamina. The larger blood vessels showed atherosclerosis with medial thinning. No necrotic arterioles were found. The tubules were almost completely replaced in some areas by fibrous tissue. Cloudy swelling with slight fatty degeneration was present. There was an increase in the interstitial connective tissue. In the pancreas and the liver arteriosclerosis

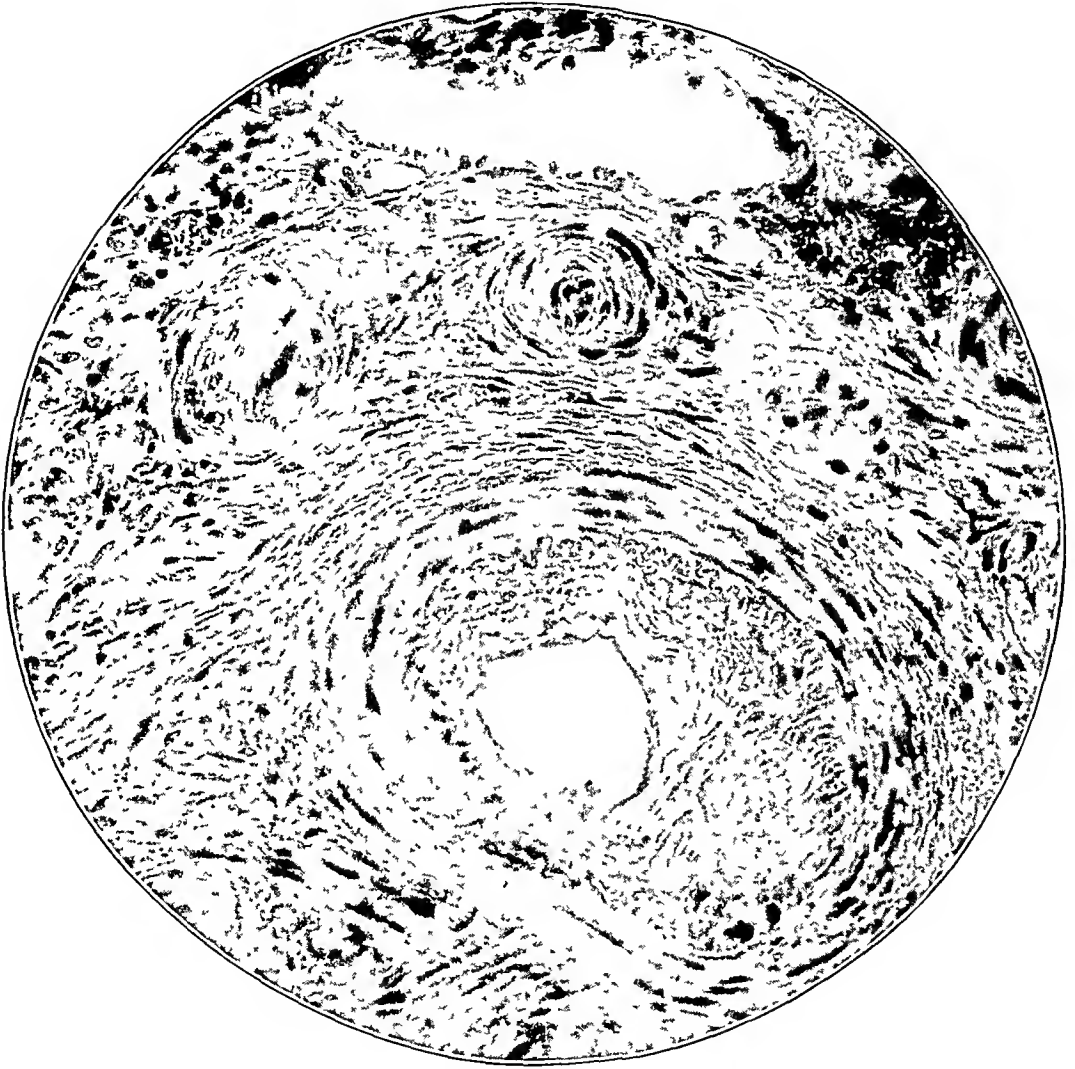


Fig. 5 (case 11).—Two arterioles and one small artery obtained from the kidney. The lumina of the three vessels are partially or totally occluded. Proliferation of the intima of the artery and degenerative changes in the wall of one arteriole, with hypertrophy of the media of the others, are to be noted.

narrowed the lumina of the smallest arteries and arterioles. There was a profound increase of the connective tissue in the spleen. The entire arterial tree was the seat of a well developed arteriosclerosis, causing occlusion of many of the finer arteries and arterioles. Sections from the pectoralis major showed no abnormal changes. The smallest arteries and arterioles of the lung were normal.

CASE 12.—J. R., a white woman, aged 50, entered the hospital on March 18, 1929, complaining of shortness of breath for the previous year. The blood pressure was 240 systolic and 120 diastolic. The radial and temporal arteries were small and wiry. There was no renal impairment. Heart failure was well developed. Ophthalmoscopic examination showed: edema of both disks, with many large petechial hemorrhages throughout the retina. The Wassermann reaction of the blood was negative. The patient appeared to be improving, when on March 22 she died suddenly.

Autopsy revealed the heart eccentrically hypertrophied to the left; it weighed 415 Gm. The valves were intact. There was atherosclerosis of the aorta. The coronaries were arteriosclerotic but not occluded. About 9 cm. above the area of the aortic valve there was a tear which penetrated between the intima and media. This dissecting aneurysm occupied the entire aortic wall down to the abdominal section. Both kidneys were smaller than normal, the right one weighing 105 Gm., and the left 95 Gm. The surface was finely granular. On cut surface the cortex was found to be thinned; the blood vessels were thickened and gaping. On microscopic examination, most glomeruli were found to be normal, while some were fibrosed; no necrotic loops were seen. In the epithelial cells of a few convoluted tubules were fatty deposits, none of which doubly refracted polarized light. The arterioles were universally narrowed, and in places they were occluded by the intimal thickening. Some of the arterioles showed fatty degeneration of their walls; the changes could be seen to involve all layers of the walls, occasionally with an aneurysmal dilatation of the vessels. The outstanding change in the arterioles and smallest arteries was a proliferation of the connective tissue of the intima. The elastic tissue was decidedly increased. Occasionally the media of the arterioles was thickened; usually it was atrophic. The changes in the arteries and arterioles of the liver were duplicated in the spleen and pancreas, where there was arteriosclerosis. Sections from the pectoralis major revealed hypertrophy of the media and adventitia; the intima was normal. No abnormal changes were found in the smallest arteries and arterioles of the lungs.

CASE 13.—A. M., a white laborer, aged 24, entered the hospital on July 26, 1927. His only complaint was headache. About one month prior to entrance he began to have pain in the back of the neck which slowly progressed into a headache that usually lasted all day and that disappeared at night. The past history was irrelevant except that the patient had had scarlet fever in childhood. He was well developed, and from all appearances seemed to be in good physical condition. The blood pressure was 264 systolic and 178 diastolic. No edema was present. The heart was in its normal position and the sounds were normal. Ophthalmoscopic examination revealed an exudative choroiditis; the veins were full and tortuous. The arteries were thin. Both disks were extensively swollen with edema. Fresh choroidal exudates were found around the fundi. In the macular area were old exudates with pigmentation. Petechial hemorrhages were present throughout. The Wassermann reaction of the blood was negative. The nitrogen content of the blood rose rapidly, especially toward the close of life. No dyspnea or edema developed. The course of the disease was followed until the patient died of renal insufficiency in December.

CASE 14.—M. K., a white woman, aged 47, entered the hospital on Feb. 2, 1929, complaining of headache, pain in the epigastrium and nocturia for the previous five months. No accurate data concerning the patient's past record could be obtained. The blood pressure was 230 systolic and 120 diastolic. The radial arteries were small, wiry and difficult to compress, but not tortuous, and the walls

were slightly thickened. Renal function was not impaired. Cardiac hypertrophy was moderate. Ophthalmoscopic examination showed the arteries to be thin and straight and the veins full. Many hemorrhagic areas were seen throughout both retinas; there was edema of both disks. The headaches became more severe; the patient lost 15 pounds (6.8 Kg.) in weight in two months, and her vision gradually failed. The Wassermann reaction of the blood was negative; no anemia was present. A biopsy of the pectoralis major muscle showed pronounced thickening of the media of the arterioles and smaller arteries; the lumen of all the arterioles were almost obliterated. There was a slight hyperplasia of the elastic tissue of the arteries, but the intima was practically normal.

CASE 15.—H. W., a white housewife, aged 38, was seen first on March 12, 1929. For the previous six months she had had edema of the ankles and face, profound dyspnea, severe headaches and visual disturbances with loss of vision at times. The symptoms became progressively worse. The family history was of interest in that the mother died of heart failure and the father of an apoplectic stroke. Of the four sisters living, two had blood pressures of over 180 systolic and 110 diastolic; of two brothers, one had a hypertension of 210 systolic and 125 diastolic. Urinalyses and an ophthalmoscopic examination of these six members of the family failed to show abnormalities. The patient had had hypertension for at least one year prior to the present complaint, and the urine had been pronounced normal on numerous occasions until two months prior to the present observation. The blood pressure was 240 systolic and 130 diastolic. The radials and temporals were not tortuous; the arterial walls were under great tension, but no more than slight thickening of the walls was found. The renal function was moderately reduced. The heart appeared to be normal. There was a pronounced edema of the legs, abdomen and face. Ophthalmoscopic examination showed that the arteries were tortuous; both disks were edematous, and many hemorrhages were seen in the peripheral zones. The Wassermann reaction of the blood was negative. The headaches became severe. The blood pressure persisted, and the patient gradually became worse. Permission to perform a biopsy on muscle was not granted.

CASE 16.—G. Z., a white girl, a factory worker, aged 19, was admitted to the hospital on July 5, 1925, with the complaint of severe headaches for one week. For four months she had suffered from nervousness, dyspnea and palpitation of the heart. The blood pressure was 256 systolic and 140 diastolic. Renal function was normal. The left border of the heart extended well outside its normal position; the apex beat was in the sixth intercostal space. A loud systolic murmur was found at the mitral, and a diastolic at the aortic, area. She was confined to bed because of weakness, dyspnea and headache. Ophthalmoscopic examination revealed pronounced edema of both disks, and many petechial hemorrhages in the retina of both eyes. The Wassermann reaction of the blood was negative. After two weeks in the hospital, the patient left against advice and has not been heard from since.

PRIMARY CARCINOMA OF THE LIVER *

G. F. STRONG, M.D.

AND

H. H. PITTS, M.D.

VANCOUVER, CANADA

The comparative infrequency of primary carcinoma of the liver would seem to justify this report of nine such cases occurring at the Vancouver General Hospital during the years from 1920 to 1927, inclusive. During this period other cases occurred in which such a diagnosis was made, but these have been excluded from the present series either because of an incomplete autopsy or because the microscopic observations were open to question. The nine cases here reported are, we believe, undoubted instances of primary carcinoma of the liver.

At one time thought to be a common condition, true primary carcinoma of the liver is now known to be comparatively rare. Secondary involvement of the liver by metastasis from primary growths elsewhere, especially in the gastro-intestinal tract, is more common. No attempt will be made here to enter into any extensive discussion of the subject because of the excellent articles already available. In 1926, Counsellor and McIndoe,¹ in a report of five cases from the Mayo Clinic, included an excellent discussion and bibliography to that date.

As far as the gross appearance is concerned, primary carcinoma of the liver is divided into massive, nodular and diffuse. Microscopically, these growths are of two types; hepatoma or true liver cell carcinoma and cholangioma or bile duct carcinoma. Six of these nine cases are true hepatomas and three are cholangiomas. Of these nine cases, eight were in Chinese and one in a white man. This considerably greater incidence of the disease in the Chinese seems worthy of some consideration. When this was first noted by one of us (G. F. S.) it was thought that the larger percentage of autopsies in our Oriental patients might account for this observation. This is not the case, however, for, while it is true that the percentage of autopsies in Chinese is practically twice that in white patients, at the Vancouver General Hospital, the much smaller number of Chinese admitted to that institution would only further emphasize the strikingly high incidence of primary carcinoma of the liver among these people.

* Submitted for publication, Aug. 21, 1929.

1. Counsellor, V. S., and McIndoe, A. H.: Primary Carcinoma of the Liver, *Arch. Int. Med.* **37**:363 (March) 1926.

In table 1 we have summarized the number of deaths and the autopsies occurring at the Vancouver General Hospital in the white and in the Chinese patients.

During the eight years (1920 to 1927), 1,024 autopsies were performed, with the observation of nine cases of primary carcinoma of the liver, giving an incidence of 0.87 per cent, which we realize is high as compared with other series. Counsellor and McIndoe, in reviewing a large series of reported cases, noted an incidence of 0.14 per cent in 42,276 autopsies. When our figures are analyzed and the white people and Chinese are separated, the incidence as far as the white man is concerned more nearly approximates this reported figure. In the 909 autopsies on white patients, primary carcinoma of the liver was found only once, giving an incidence of 0.11 per cent. In the

TABLE 1.—*Summary of Deaths and Autopsies at the Vancouver General Hospital*

Year	Total Deaths	White Deaths	White Autopsies		Chinese Deaths	Chinese Autopsies	
			Number	Percentage		Number	Percentage
1920.....	688	641	113	17.6	47	19	40.4
1921.....	598	568	121	21.3	30	12	40.0
1922.....	654	598	126	21.0	56	19	33.9
1923.....	552	513	124	24.1	39	10	25.6
1924.....	557	508	78	15.3	49	17	34.6
1925.....	663	616	95	15.4	47	13	27.6
1926.....	689	641	133	20.7	48	16	33.3
1927.....	738	714	119	16.6	24	9	37.5
	5,139	4,799	909	19.0	340	115	34.1
				average			average

Total autopsies, 1,024.

Chinese series, among 115 autopsies the finding of eight such cases gives an incidence of 6.9 per cent. Because of this unusually high incidence, we have felt keenly the necessity of being absolutely certain of our observations before making any report. In order to check our results, we have submitted our material to Dr. William Boyd, professor of pathology at the University of Manitoba, who has reviewed the microscopic sections and has had the accompanying photomicrographs prepared. We have included in our report only those cases about which there appeared to be no doubt.

While it has been difficult to obtain accurate statistics from China as to disease incidence, such information as has been collected would indicate that there is an increased frequency of chronic diseases of the liver especially in southern China. The Chinese immigrants to British Columbia come from the southern province of Kwantung, and to make comparative figures of any value, it was necessary to secure data from that part of the country. There are no autopsy series available from Canton, but some interesting facts have been revealed. Dr. W. W.

ing feature of his cases from Singapore is the high frequency of primary carcinoma of the liver among the Javanese as well as the Chinese (and mentioned that in 90 per cent of their cases the carcinoma occurs in cirrhotic livers). One reason for the high incidence of chronic disease of the liver is the increased occurrence of intestinal diseases, especially the high incidence of infection with parasites. *Schistosoma* produced a definite type of cirrhosis of the liver. Liver fluke, *Clonorchis sinensis*, is another common parasite in southern China and has been noted as the cause of cirrhosis and even carcinoma of the liver. Nauck and Liang⁶ recently reported from Shanghai the case of a young Chinaman with primary carcinoma of the liver and an accompanying infection with *Clonorchis*. These authors reviewed the interesting etiologic relationship between helminths and tumor growth, pointing out that nematode worms have been said to produce tumors in the stomachs of rats, that *Bilharzia* have produced malignant tumors of the bladder and that tumors of the liver have been attributed to *Schistosoma*. They also reviewed the other reported cases of primary carcinoma of the liver said to result from infection with *Clonorchis*. They pointed out that, while the increased incidence of chronic disease of the liver is not due alone to infection with *Clonorchis*, the common observation of chronic intestinal disease, including intestinal parasites, must be considered as an important factor in the production of these conditions of the liver. They concluded that the relatively high frequency of carcinoma of the liver in eastern Asia may be attributed to the prevalence of injuries to the liver resulting from the chronic inflammatory irritation leading to chronic hepatitis and cirrhosis of the liver. They also believe that infection with *Clonorchis* is one cause of primary carcinoma of the liver in China. Faust⁷ studied the epidemiology of infection with *Clonorchis* and showed that it was never found in the north, occasionally occurred in central China, but was most common in the south, in the Province of Kwantung (where raw fish is eaten). As already mentioned, Chinese immigrants to British Columbia come almost entirely from Kwantung. These Chinese are commonly infected with liver fluke, though, it is rarely a cause of any demonstrable disability. In fact, clonorchiasis is not considered contagious, and aliens are not excluded because of the presence of the parasite unless the disease has affected the ability to earn a living.

One of the nine cases is presented here in detail as the patient was studied in the hospital for nearly four months before his death, and an antemortem diagnosis of primary carcinoma of the liver was made.

6. Nauck, E. G., and Liang, B.: Primärer Leberkrebs und *Clonorchis* Infektion. Arch. f. Schiffs- u. Tropen-Hyg. **32**:109 (March) 1928.

7. Faust, E. C.: Some Recent Aspects of the Epidemiology of *Clonorchis* Infection in China, China M. J. **39**:287, 1925.

The diagnosis was based largely on our previous frequent observation of this condition in Chinese patients. The other eight cases are presented briefly. It is to be regretted that the clinical details of these cases are so meager. Frequently, however, the patient was moribund or nearly so on admission and no history was obtainable.

REPORT OF CASES

CASE 1.—History.—Q. S., a Chinese laborer, aged 45, was admitted to Vancouver General Hospital on Oct. 22, 1926, complaining of swelling of the abdomen and legs and progressive weakness. The past history revealed nothing of importance. He had lived in Canada for twenty years.

In January, 1926, while working on a railroad near Prince Rupert, B. C., the patient became weak and felt unable to work. He consulted a local physician who could not determine the cause of his complaints. In July, he noticed that his abdomen was larger than usual, and he later noticed a rather tender lump in the right part of the epigastrium. He went to Vancouver in August, getting progressively weaker and steadily losing weight. His usual weight was 128 pounds (51.8 Kg.); the weight on admission was 110 pounds (49.9 Kg.).

Examination.—Examination revealed an emaciated, middle-aged Chinese man, unable to lie flat in bed because of shortness of breath. The heart was normal. The lungs were clear, with some dulness at the base of the right side. The abdomen was considerably enlarged by a tense collection of free fluid. After paracentesis of 70 ounces of chyloform ascitic fluid, a slightly tender nodular mass could be felt in the epigastrium and right hypochondrium. This mass was apparently the liver, although there was no general downward enlargement of that organ. Liver dulness extended upward in the right side of the chest to the level of the third rib. The liver was fixed, not coming down with inspiration or change of position. The spleen was not enlarged. No other masses or tenderness were present.

The results of the rectal examination were negative.

The nervous system was normal.

There was considerable edema of the legs and feet.

Laboratory Observations.—On repeated examination, the urine showed a trace of albumin and occasional hyaline casts. The Wassermann reaction of the blood was negative. The nonprotein nitrogen was 33 mg. per hundred cubic centimeters of whole blood. The blood count showed: red cells, 3,602,000; hemoglobin, 70 per cent; white cells, 5,500; polymorphonuclears, 76 per cent; lymphocytes, 24 per cent.

Roentgen examination showed the gastro-intestinal tract to be normal. There was no roentgen evidence of gastric carcinoma.

Fluoroscopic examination showed the right side of the diaphragm to be very much elevated, apparently as a result of an enlarged liver. Stereoroentgenograms of the lungs showed them to be clear. The right side of the diaphragm was elevated to the second rib.

Because of our previous observation of primary carcinoma of the liver in the Chinese, the condition of this patient was so diagnosed.

The patient remained in the hospital until his death on Feb. 13, 1927. The clinical course of his condition was typical of that associated with rapidly progressive cirrhosis of the liver. Six tappings were necessary to relieve the recurring ascites. In this case, merbaphen as a diuretic was remarkably effective and

had it not been for this drug more frequent drainage of the ascitic fluid would have been necessary. He was given 1 cc. of merbaphen intravenously every three days for nearly two months. Part of this time the merbaphen was accompanied by ammonium chloride. The acid salt did not appear to increase the effectiveness of the mercury diuretic—as even without ammonium chloride a definite diuresis occurred after each administration of the merbaphen. There was no change in renal function as a result of the long continued use of merbaphen as judged by urinalysis, phthalein excretion and nonprotein nitrogen of the blood.

Autopsy Report.—The body was that of a very emaciated, fairly well developed, Chinese man. The abdomen was considerably distended and apparently contained fluid. The lower part of the abdomen showed a number of small paracentesis wounds. Otherwise, external examination was negative. The usual midline incision from the manubrium to the symphysis was made and a great deal of somewhat chylous ascitic fluid poured forth from the abdominal cavity. The right lung was very firm in its lower half and seemed to be contiguous with the liver. The right lower lobe was completely compressed. The upper portions of the lung, that is, the middle and upper lobes, were slightly compressed, but still crepitant. The reason for the compression of the right lower lobe was seen to be due to an extremely large growth originating in the liver which had grown up through the diaphragm on the right and produced an upward displacement of the diaphragm and the lower lobe of the lung. It had not, however, invaded the lung tissue proper. The upper aspect of the growth was domelike and regular. On section it presented a somewhat lobulated grayish-white, firm, slightly bile-tinged carcinomatous appearance. The right lobe of the liver was generally involved, but a number of nodules were also present in the left lobe. A great deal of compression apparently had occurred on the portal system. The gallbladder, stomach, duodenum, prostate and intestinal tract did not show any evidence of new growth, which would account for the original focus with metastases to the liver. The left lung was relatively intact. The heart was removed without detaching it from the right lung and it was found that a projection of the growth, the size of a hen's egg, was present in the right auricle between the superior and inferior venae cavae. The abdominal viscera showed no particular evidence of any lesion beyond considerable passive venous congestion. Further examination of the body was negative. The diagnosis was primary carcinoma of the liver with extension through the right side of the diaphragm to the right pleural cavity and right auricle.

Chylous ascites was present.

Microscopic Observations.—Section through the tumor mass in the right pleural cavity and through the masses in the liver all showed a similar picture characterized by many cordlike aggregations of large, atypical, hyperchromatic cells, the nuclei of which showed frequent mitoses. They exhibited an unrestricted fashion of growth and were grouped about alveolar spaces as though attempting duct formation. Many of these spaces contained a homogeneous pinkish-staining, colloid-like material. A relatively dense cirrhosis prevailed throughout and many areas of degeneration and hemorrhagic extravasation were also evident.

Diagnosis.—The diagnosis was primary carcinoma of the liver (cholangioma type).

CASE 2.—Jung Yen, a Chinese laborer, aged 33, was admitted to the hospital on June 18, 1920. No history was obtainable. He presented marked edema of the feet, legs and abdomen. The liver was enlarged and nodular. The patient lived only one and one-half hours after admission to the hospital.



Fig. 1 (case 1).—The nodule in the right auricle. A portion of the liver, the right lung and the right auricle is shown. A mass of carcinomatous tissue, the size of a hen's egg, is shown projecting into the right auricular chamber. This is not metastatic but is a direct extension of the primary growth of the liver which had pushed through the diaphragm and lung tissue and finally the auricular wall.

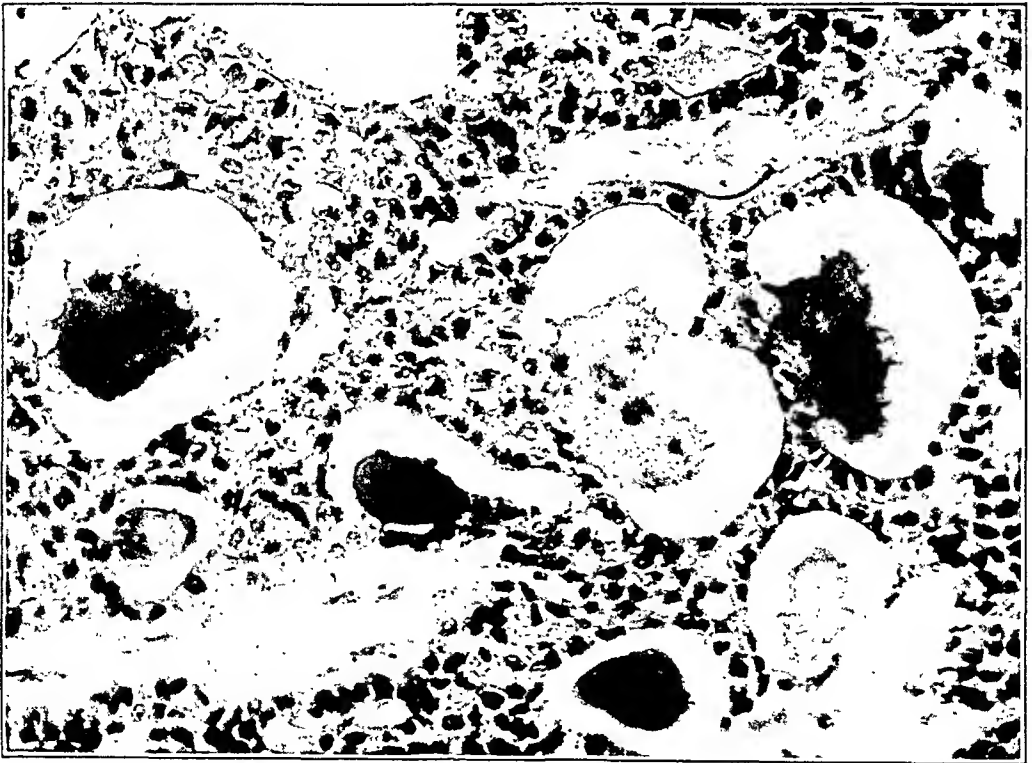


Fig. 2 (case 1).—Section of the tumor; $\times 175$. "The tumor cells, although in places arranged diffusely, are for the most part grouped around alveolar spaces—the cells are fairly uniform in size. I should be inclined to class this as a bile duct carcinoma" (Dr. William Boyd).

Autopsy Report.—There was marked edema of the lower extremities and ascites. The liver weighed 6,650 Gm. There were grayish-white nodules of varying size, from 1 to 6 cm. in diameter, almost all in the right lobe. The intervening liver tissue was grossly cirrhotic. Metastatic nodules were present in both lungs. No evidence of other primary growth was revealed on further examination.

Microscopic Observations.—In this tumor the cells were not as large as those seen in several of the other tumors of this series. They were slightly pleomorphic, and the nuclei were hyperchromatic, pyknotic and mitotic. The cells were arranged in solid, relatively small aggregations with no attempt at acinar or duct formation, and in one area a definite tumor embolus was seen in a large vein. A well defined cirrhosis was present throughout.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

CASE 3.—Yee Mah, a Chinese laborer, aged 45, was admitted to the hospital on March 11, 1921. The past history revealed nothing significant. For fourteen months he had suffered from loss of weight and pain in the upper part of the abdomen, with occasional attacks of fever.

The patient was emaciated, with definite ascites and edema of the feet and legs. The liver was enlarged. He died on April 4.

Autopsy Report.—There was edema of the lower extremities. The peritoneal cavity was filled with bloody fluid. The liver weighed 4,970 Gm. The right lobe almost completely replaced by large, grayish-white tumor masses, one, superficially placed, being extremely degenerated and hemorrhagic, apparently the source of the intraperitoneal hemorrhage. The left lobe was also studded with smaller nodules, many of which were bile stained, the intervening liver substance being cirrhotic. Metastatic nodules were found in the lungs, omentum and brain. No other primary growth was found on further examination of the body.

Microscopic Observations.—Sections through the tumor tissue showed it to consist of an aggregation of large, atypical, pleomorphic, hyperchromatic cells, many of which were extremely large with multinucleation and mitoses. In some areas the cells were arranged in fairly compact masses, in others more loosely arranged, but on the whole the stroma was sparse and fairly general degeneration was apparent throughout. Definite periportal cirrhosis was in evidence.

Diagnosis.—The diagnosis was primary carcinoma of the liver with cirrhosis (hepatoma type).

CASE 4.—Gee Yuen, a Chinese laborer, aged 57, was admitted to the hospital on Jan. 17, 1921. He presented swelling of the feet and abdomen, weakness and loss of weight for one month. Ascites and edema of the feet were present. He died on January 24.

Autopsy Report.—Relatively little of note was found on external examination. There was no edema of the extremities or ascites. The peritoneal cavity was filled with clotted and fluid blood. The omentum was adherent apparently by recent adhesions to a mass in the inferior aspect of the right lobe of the liver in which a deep hemorrhagic split was present, evidently the source of the hemorrhage. The liver weighed 3,060 Gm. It had been converted into a rather sclerotic, yellowish-white mass with relatively little normal liver tissue present, with areas of necrosis throughout. Finger-like processes of tumor tissue were found protruding into the inferior vena cava. No metastases were found in the lungs, etc., and there was no evidence of other primary growth elsewhere in the body.

Microscopic Observations.—The cells were large, fairly uniform, hyperchromatic and atypical; the nuclear material was especially dense but the cells generally showed none of the giant-like forms seen in many of the hepatoma types. They were arranged about definite, variously sized, ductlike spaces while in many areas definite tumor emboli were seen within vascular channels. Degenerative and inflammatory changes were in evidence with a definite but relatively fine cirrhosis throughout.

Diagnosis.—The diagnosis was primary carcinoma of the liver (cholangioma type).

CASE 5.—Lim Hong Kit, a Chinese laborer, aged 47, was admitted to the hospital on June 24, 1922. No history was obtainable. He complained of ascites and edema of the legs. He died on June 25.

Autopsy Report.—There was some edema of the lower extremities. The peritoneal cavity was filled with serosanguineous fluid. The liver weighed 2,400 Gm. and was markedly cirrhotic in appearance, with many smaller and larger grayish-white nodules scattered throughout, chiefly in the right lobe. In one area, a process of tumor tissue protruded into the right portal vein. Several grossly involved perigastric lymph glands were present. There was no evidence of further metastases or other primary growth on further examination.

Microscopic Observations.—The cells were pleomorphic, generally pale staining and arranged in solid sheets surrounding spaces which were evidently vascular sinuses lined by elongated endothelial cells apparently of the Kupffer type. In other areas, aggregations of dissimilar cells were seen which were of relatively enormous size, pale and with multinucleation into many bizarre formations. Dense fibrotic bands surrounded these areas while in the former areas definite but finer cirrhosis was evident.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

CASE 6.—Hong Chip, a Chinese laborer, aged 21, was admitted to the hospital on Nov. 5, 1922. Six days before admission he noted anorexia, headache and increasing vomiting. He was in coma at the time of admission. He died two days later.

Ascites were present; the liver was palpable. There was no edema of the feet.

Autopsy Report.—There was no edema or ascites. The liver weighed 1,950 Gm. A single, large, grayish-white mass almost completely replaced the right lobe of the liver with a few smaller discrete nodules surrounding it. No metastases were found and no other primary growth was revealed on further examination of the body.

Microscopic Observations.—The tumor cells were uniform in size, rather small and for the most part surrounded gland or ductlike spaces, many of which were very elongated. Mitotic figures were numerous, but none of the very large cells were seen. A moderate amount of coarse cirrhosis was present throughout.

Diagnosis.—The diagnosis was primary carcinoma of the liver (cholangioma type).

CASE 7.—Lim Lap Fon, a Chinese laborer, aged 53, was admitted to the hospital on May 15, 1923. Extreme emaciation was evident. There was no edema of the extremities. The liver was slightly enlarged. There were no ascites. The patient died on May 26.

Autopsy Report.—External examination gave negative results. There was no ascites or edema. The liver weighed 2,000 Gm. and was studded with grayish-

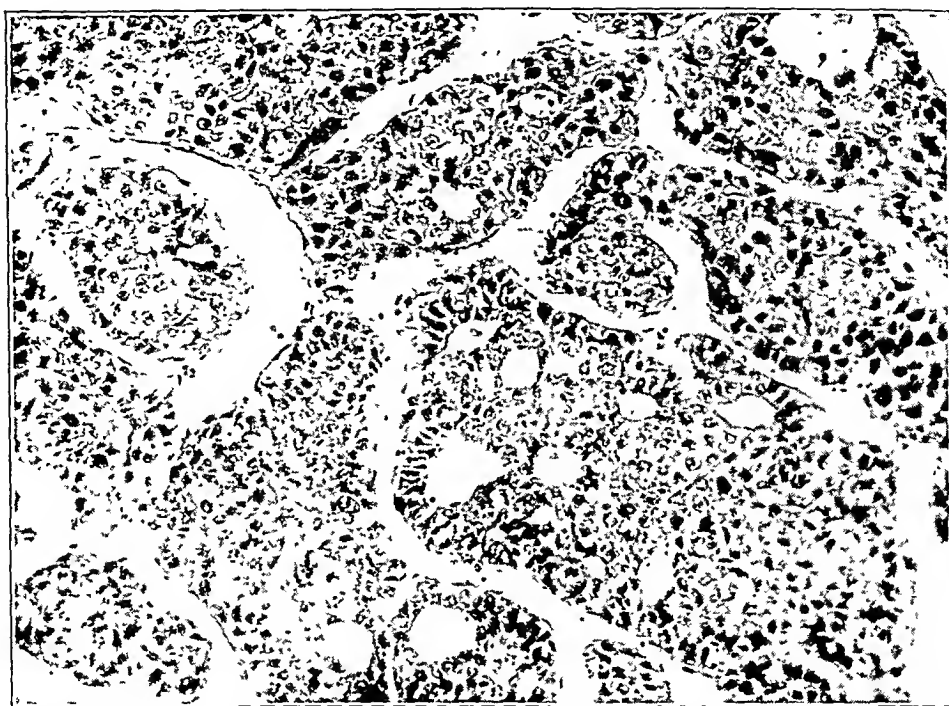


Fig. 3 (case 4).—Section of the tumor; $\times 125$. "The photomicrograph shows very clearly the early picture of bile duct carcinoma, with a certain arrangement of cells around ductlike spaces" (Dr. William Boyd).

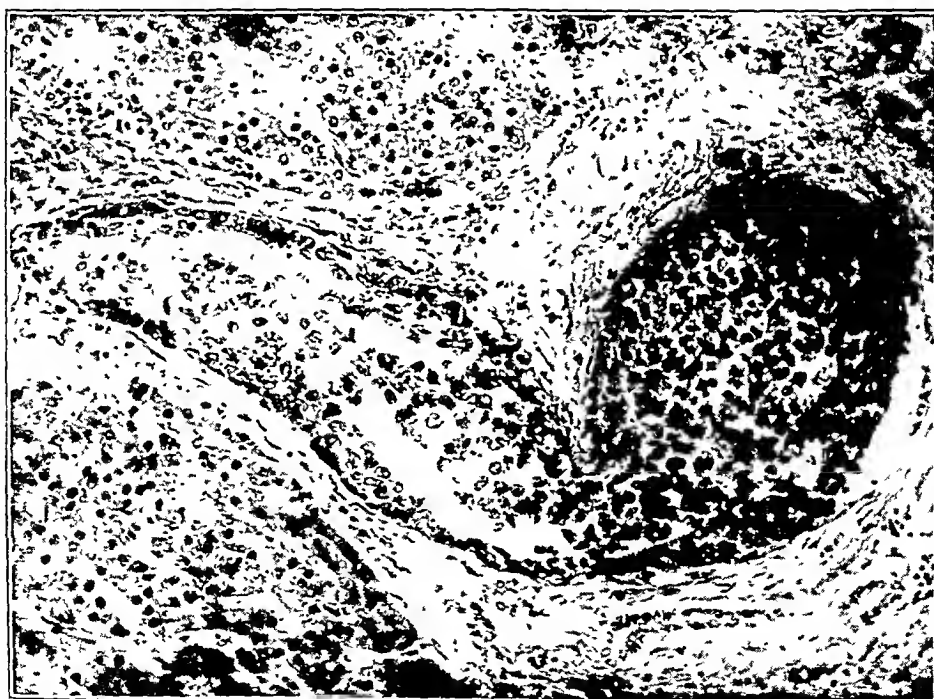


Fig. 4 (case 4).—Tumor embolus; $\times 125$. Extension of the tumor.

white nodules from 2 mm. to 2 cm. in diameter throughout both lobes. A few smaller, similar nodules were present in the spleen. Several metastatic nodules were found in three of the left ribs. No other primary growth was found on examination of the remainder of the body.

Microscopic Observations.—Throughout these sections many cords and columns of pleomorphic cells of liver type were seen. Many of them were extremely large, with correspondingly large nuclei in which mitotic figures were frequent. Interspersed throughout one saw well defined bands of fibrous tissue of cirrhotic type in which fairly numerous but well developed biliary ducts were present.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

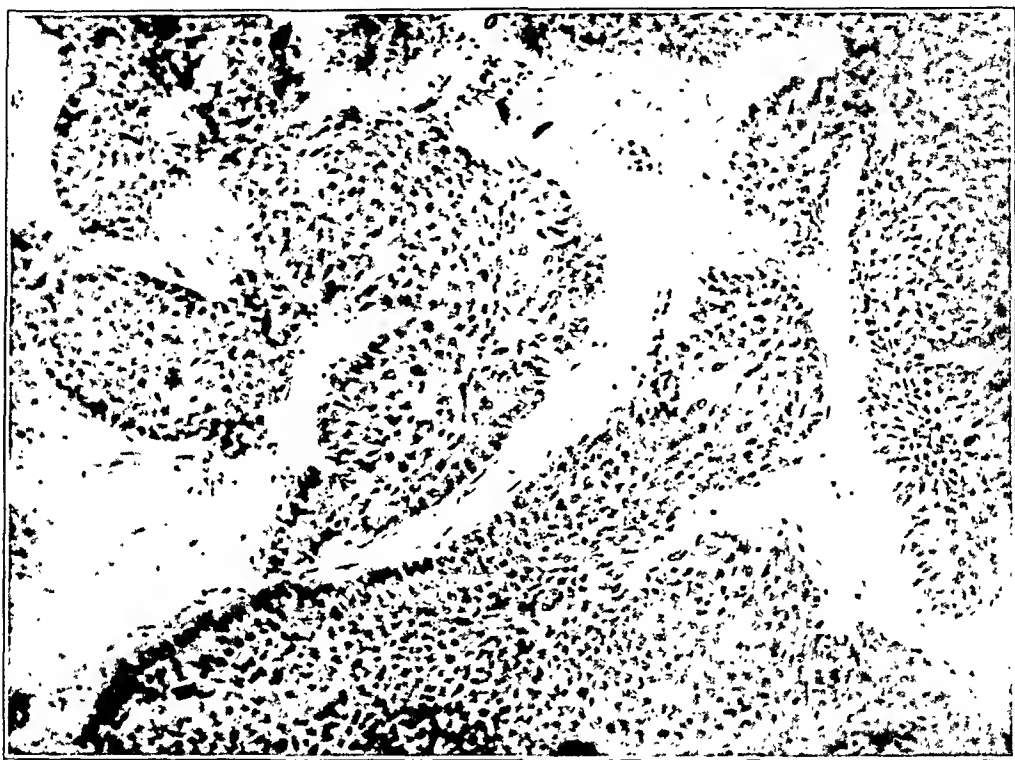


Fig. 5 (case 6).—Section of the tumor; $\times 125$. "Most of the section is composed of sheets of cells resembling liver cells, the sheets being separated by large spaces, probably blood spaces. These spaces are lined by very distinct endothelial cells which apparently represent unusually distinct Kupffer's cells. In addition to the sheets, there are a few areas quite different in appearance, composed of huge, pale, multinucleated cells, similar to those seen in other primary liver cell tumors. The latter areas are surrounded by dense fibrous tissue" (Dr. William Boyd).

CASE 8.—McM., a white laborer, aged 76 years, was admitted to the hospital on July 12, 1926. He had had weakness for two years. The edema of the feet, legs and abdomen was getting gradually worse. He was comatose at the time of admission. He died on July 13.

Autopsy Report.—There was edema of the lower extremities. Serosanguineous fluid was present in the peritoneal cavity and in both pleural cavities. The liver weighed 2,500 Gm. and was studded throughout with many grayish-white, bile

stained nodules, while a larger superficial mass on the superior surface of the right lobe was adherent to the hepatic flexure of the colon but did not extend into the lumen. Metastatic nodules were also present in the lungs. No other primary growth was found on further examination of the body.

Microscopic Observations.—The picture presented in the sections from this tumor was practically identical with that seen in case 7, with the exception of an almost complete absence of cirrhotic changes. This would seem to be rather of interest owing to the fact that it is from the only white man in our series and the only patient showing no cirrhosis.

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

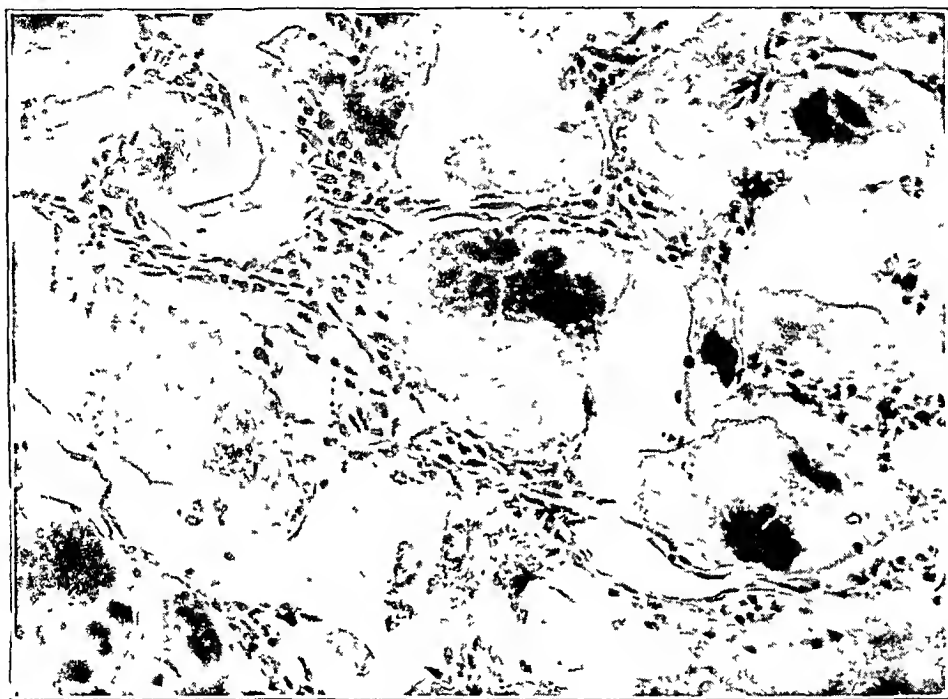


Fig. 6 (case 6).—Section of the tumor, showing large multinucleated cells surrounded by dense fibrous tissue; $\times 200$.

CASE 9.—Leung Ling, a Chinese laborer, aged 35, was admitted to the emergency ward in an unconscious state on Sept. 5, 1927, and died within a few minutes after admission.

Autopsy Record.—The body was that of a well developed and nourished Chinese man. Nothing remarkable was apparent on external examination. The peritoneal cavity was completely filled with clotted and fluid blood, the source of which was found at the margin of the lower portion of the right lobe of the liver where a large degenerated carcinomatous mass, 8 by 6 cm., had eroded a large blood vessel, the thrombosed end of which was apparent. The liver was small, weighing only 1,090 Gm. It was markedly cirrhotic. In the right lobe many grayish-white nodules, varying in size from that of a filbert to that previously noted, were seen, all more or less degenerated in appearance. The left lobe was free from nodules. A large tumor embolus was present in the first portion

of the inferior vena cava. No gross metastases were found, and further examination of the body revealed no other primary growth.

Microscopic Observations.—Sections through the liver showed the presence of many aggregations of atypical liver cells, some of which appeared to be from eight to ten times the size of the normal cells, irregular in shape, with large, single or multiple hyperchromatic nuclei frequently showing mitosis. No attempt at acinar or duct formation was apparent although in a few areas the cells were arranged in solid cylindric formations frequently showing considerable central degeneration. Extensive cirrhosis was present throughout with dense bands of fibrous tissue surrounding masses of these atypical cells. No tumor emboli were evident in the sections.

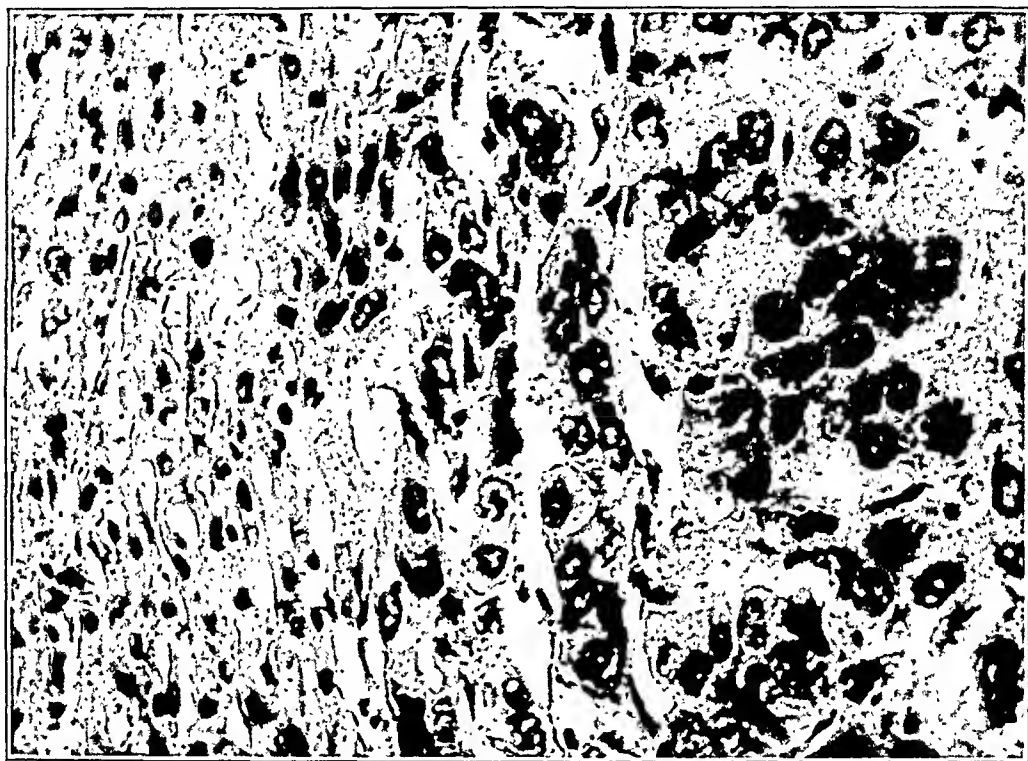


Fig. 7 (case 7).—Section of the tumor; $\times 300$. "Scattered throughout the section of the liver are numerous large tumor masses, which are composed of irregular cords of cells the general structure and arrangement of which resemble that of normal liver tissue. Many of the cells are very large and possess huge nuclei. There are numerous mitotic figures. In some places the tumor cells can be seen to arise from the liver cells. There is a well marked cirrhosis and in the cirrhotic material are numerous new bile ducts. These do not show any evidence of malignant neoplasia. This is evidently a hepatoma with cirrhosis" (Dr. William Boyd).

Diagnosis.—The diagnosis was primary carcinoma of the liver (hepatoma type).

COMMENT

Sex and Age.—All nine cases occurred in males. The fact that eight Chinese patients were men may or may not be of some significance. The much smaller number of Chinese women living in British Columbia

would account in part for this sex incidence. The definite preponderance of males suggests some environmental factor.

The average age in this series was 45.6 years with extremes of from 21 to 76 years.

Symptoms.—There are no symptoms pathognomonic of this condition. The clinical picture presented is that of a rapidly progressing cirrhosis of the liver. It is not possible to diagnose with accuracy primary carcinoma of the liver without a complete autopsy. The common symptoms are weakness, loss of weight, ascites, swelling of the feet and legs and gastro-intestinal disturbances; vomiting or diarrhea may occur. Jaundice is not a constant occurrence. One feature which we believe is rather common is the fact that the liver becomes fixed, and frequently enlarges upward to a greater extent than downward. The fixation is apt to occur early, and the upward enlargement is favored by the fact that the diaphragm and right lung present less resistance than the fluid-filled peritoneal cavity. Because of the fixation and upward enlargement of the liver, the fact of enlargement may be

TABLE 2.—*Age Incidence*

Decade	Chinese	White
21 to 30.....	1	0
31 to 40.....	2	0
41 to 50.....	3	0
51 to 60.....	2	0
61 to 70.....	0	0
71 to 80.....	0	1

overlooked since it is customary to estimate liver enlargement by the degrees of the extension of its lower boarder below the costal margin. The result of fixation and upward enlargement was clearly shown in case 1 in which roentgen examination showed the dome of the liver up to the second rib.

Pathology.—As mentioned before, primary carcinoma of the liver may be divided into two types on the basis of the cellular pathologic changes: (1) hepatoma, a true liver cell tumor, and (2) cholangioma, a bile duct tumor. The histologic features of these two types of carcinoma are described in connection with the cases here presented and in the description of the accompanying photomicrographs. Further discussion of these observations is unnecessary. In this series, there were six hepatomas and three cholangiomas.

The relation of cirrhosis to primary carcinoma of the liver is definitely established. Counseller and McIndoe went so far as to question the diagnosis of a primary carcinoma of the liver in the absence of a definite cirrhosis. The cirrhosis may be either portal or biliary and is probably a precursor of the carcinoma. In cirrhosis, a degeneration of the liver cells and bile ducts occurs followed by some evidence of

regeneration or attempts at regeneration, which may result in the disorderly growth which characterizes these carcinomas. Eggel⁸ found cirrhosis in 85 per cent of hepatomas and 50 per cent of cholangiomas. In our series, cirrhosis was present in all three of the cholangiomas and in five of the six hepatomas, the exception being in the only white patient in the series.

Metastases appear to occur entirely by the blood stream. The hepatomas invade the capillaries, and gross tumor emboli are frequently seen in these cases in portal vein radicals and in the inferior vena cava. The cholangiomas are said to metastasize earlier and more frequently than the hepatomas. In this series, however, metastases were more frequent among the hepatomas, occurring in five of the six cases, and being found in only one of the three cholangiomas. The lungs were involved in four cases, the ribs and spleen in one case, the mesenteric and perigastric glands in one and the brain in one. The nodule shown in figure 2 is not a metastasis but rather an extension of the tumor substance into the cavity of the right auricle.

Of some interest is the fact that three of our patients died suddenly as a result of extensive intraperitoneal hemorrhage caused by erosion of a large vessel by a tumor nodule. Similar observations have been reported by Karsner.⁹

While nothing has been added to our knowledge of primary carcinoma of the liver by this contribution, it seemed worthy of record: (1) because of the rather large number of cases of a comparatively rare condition and (2) because of the high incidence in the Chinese. This increased incidence in the Chinese in our series is, we believe, a result of the fact that these immigrants come from Kwantung, a province in China where chronic disease of the liver and primary carcinoma of the liver are of more frequent occurrence than in other parts of China. Infection with *Clonorchis* may have been the exciting factor in the production of some of these primary carcinomas, while others may have resulted from chronic irritation of the liver due to other causes (hepatitis with resulting cirrhosis). While the actual parasites were not found in any of our cases, the infection with *Clonorchis sinensis* is after all only the exciting factor, the parasites setting up a chronic irritation resulting in a cirrhosis and in some cases in primary carcinoma.

8. Eggel, H., quoted by Counseller and McIndoe: Arch. Int. Med. **37**:363 (March) 1926.

9. Karsner, H. T.: A Clinicopathological Study of Primary Carcinoma of the Liver, Arch. Int. Med. **8**:238 (Aug.) 1911.

CONCLUSIONS

A series of nine cases of primary carcinoma of the liver is presented, eight of which occurred in Chinese.

These Chinese came entirely from Kwantung, a southern province of China, where liver fluke, *Clonorchis sinensis*, is common, and where chronic diseases of the liver frequently occur.

CHRONIC ARTHRITIS

BACTERIOLOGY OF AFFECTED TISSUES *

HARRY M. MARGOLIS, M.D.

Fellow in Medicine

AND

ANNA H. E. DORSEY, M.S.

Fellow in Bacteriology, the Mayo Foundation

ROCHESTER, MINN.

In an attempt to explain the etiology of nonspecific chronic arthritis, there have emerged widely conflicting opinions based, at times, entirely on clinical or laboratory observations. But in view of the lack of definitive conclusions, it seems desirable to correlate our laboratory observations with clinical observations to determine what light may be shed on this rather perplexing problem.

The opinions of most writers in recent years have begun to lean toward the primarily infectious nature of chronic arthritis. Although, admittedly, the *modus operandi* of such infections has not been clarified, a great amount of reliable data has already accumulated in support of the infectious theory. Clinically, the frequent occurrence of arthritis in the course of acute infections such as scarlet fever, typhoid fever, malta fever, ulcerative colitis, and so forth, is well recognized. The extensive researches of Rosenow¹ and his co-workers² have emphasized the rôle of focal infection in arthritis and of the elective localizing tendencies of bacteria isolated from foci of patients with arthritis. The observations of Billings³ pointed in the same direction. Indeed, the observations of many clinicians have led them to a conception of arthritis

* Submitted for publication, Dec. 1, 1929.

* Work done in the Division of Medicine and Division of Experimental Bacteriology under the direction of L. G. Rowntree, P. S. Hench and E. C. Rosenow.

1. Rosenow, E. C.: The Newer Bacteriology of Various Infections as Determined by Special Methods, *J. A. M. A.* **63**:903 (Sept. 12) 1914; The Pathogenesis of Focal Infection, *J. Nat. Dent. A.* **5**:113, 1918.

2. Meisser, J. G., and Brock, Sam: A Clinical and Experimental Study in Chronic Arthritis, *J. Am. Dent. A.* **10**:1100, 1923. Nakamura, T.: A Study of Focal Infection and Elective Localization in Ulcer of the Stomach and in Arthritis, *Ann. Surg.* **79**:29, 1924. Nickel, A. C.: The Localization in Animals of Bacteria Isolated from Foci of Infection, *J. A. M. A.* **87**:1117 (Oct. 2) 1926.

3. Billings, Frank: Chronic Focal Infection as a Causative Factor in Chronic Arthritis, *J. A. M. A.* **61**:819 (Sept. 13) 1913; Focal Infection: Its Broader Application in the Etiology of General Disease, *ibid.* **63**:899 (Sept. 12) 1914.

as an insidious infectious process, producing the most striking changes in the joints, but having as a counterpart such phenomena as debility, at times generalized lymphadenopathy, splenomegaly and anemia, and low grade fever, all indicative of a low grade infectious process. Hench⁴ aptly described these phenomena as the systemic manifestations of the disease. Attempts to substantiate the infectious nature of chronic arthritis by bacteriologic cultures of material from joints, however, have not always proved successful. Cultures from supposedly "infectious arthritis" have frequently been found sterile, and this has been adduced as proof of the noninfectious nature of the process.

In view of the relationship of the reticulo-endothelial system to bacterial infections and the manifestations of its involvement in many cases of so-called infectious arthritis, and because of its close anatomic relationship to the joint, it seemed to us that a bacteriologic study of the epiphyseal marrow underlying affected joints might yield cultures of the offending organisms more consistently than the synovial membrane or synovial fluid, to which most of the attention has been directed in the past. Accordingly, we conducted a bacteriologic study on material obtained from the joints of patients who came to operation in the Section on Orthopedic Surgery at the Mayo Clinic. Although we were primarily interested in cultures of the marrow, we also attempted cultures of excised synovial membrane, joint fluid, cartilage and the periarticular capsule.

REVIEW OF THE LITERATURE

Schüller,⁵ in 1892, described a dumbbell-shaped bacillus which he observed in stained sections of synovial membrane from cases which he designated "polyarthritis chronica villosa." In a subsequent communication,⁶ he described this organism as a gram-positive, short, plump rod showing polar granulation. Although as a rule the organisms presented the characteristic dumbbell shape, in exceptional cases they were very short with only a slight compression in the middle, so that they resembled, somewhat, diplococci. By 1906, Schüller⁷ was able to demonstrate the presence of this organism either in the joint fluid or in the synovial membrane in 150 of 230 cases of chronic villous polyarthritis.

4. Hench, P. S.: The Systemic Nature of Chronic Infectious Arthritis, *Atlantic M. J.* **28**:425, 1925.

5. Schüller, Max: Chirurgische Mittheilungen über die chronisch rheumatischen Gelenkentzündungen, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **21**:406, 1892.

6. Schüller, Max: Untersuchungen über die Aetiologie der sogenannten chronisch rheumatischen Gelenkentzündungen, *Berl. klin. Wchnschr.* **30**:865, 1893.

7. Schüller, Max: The Relations of Chronic Villous Polyarthritis to the Dumb-Bell Shaped Bacilli, *Am. J. M. Sc.* **132**:231, 1906.

Bannatyne, Wohlman and Blaxall,⁸ in 1896, demonstrated the presence of a minute gram-negative bacillus, exhibiting polar staining, in the synovial fluid of eighteen cases of "rheumatoid arthritis."

In the few sections Bannatyne⁹ was able to obtain, he found the same organism as that found by Blaxall in the cartilage, synovial membrane and periarticular tissues.

Poynton and Paine¹⁰ obtained a diplococcus from the synovial membrane in one case of arthritis and produced arthritis in two rabbits by the injection of this organism.

Fayerweather¹¹ found three types of bacteria in four positive cultures from joints. Three of these were from cases of chronic periarticular arthritis corresponding in type to Schüller's villous polyarthritis.

In 1922, Billings, Coleman and Hibbs¹² reported positive results in six of fourteen cultures of joints. Of these, five cultures showed green-producing streptococci and one culture showed hemolytic and nonhemolytic streptococci.

In the course of a bacteriologic investigation of chronic arthritis, Mutch¹³ obtained a pure culture of *Bacillus fallax* in one case.

Crowe¹⁴ favored the opinion that so-called osteo-arthritis is caused primarily by streptococci, whereas in rheumatoid arthritis a strain of *Staphylococcus albus* is the primary cause. He labeled this organism *Micrococcus deformans*, and isolated it in several instances from the bone and pannus in cases of affected joints. He expressed the belief that streptococci found in rheumatoid arthritis represent secondary invaders.

8. Bannatyne, G. A.; Wohlman, A. S., and Blaxall, F. R.: Rheumatoid Arthritis: Clinical History, Etiology and Pathology with a Report on Its Bacteriology, *Lancet* **1**:1120, 1896.

9. Bannatyne, G. A., quoted by Llewellyn-Jones, R.: Arthritis Deformans: Comprising Rheumatoid Arthritis, Osteo-Arthritis and Spondylitis Deformans, New York, William Wood & Company, 1909, p. 59.

10. Poynton, F. J., and Paine, Alexander: An Experimental Production of the Osteo-Arthritic Type of Rheumatoid Arthritis, *Tr. Path. Soc. London* **53**: 221, 1902.

11. Fayerweather, Roades: Infectious Arthritis: A Bacteriological Contribution to the Differentiation of the "Rheumatic" Affections, *Am. J. M. Sc.* **130**: 1051, 1905.

12. Billings, Frank; Coleman, G. H., and Hibbs, W. S.: Chronic Infectious Arthritis, *J. A. M. A.* **78**:1097 (April 15) 1922.

13. Mutch, N.: An Intestinal Anaerobe and Chronic Arthritis, *M. J. & Rec.* **126**:563, 1927.

14. Crowe, H. W.: Bacteriology and Surgery of Chronic Arthritis and Rheumatism with End Results of Treatment, London, Oxford Medical Publications, 1927, p. 76.

Rosenow¹⁵ cultured one or more lymph nodes which drained inflamed joints in fifty-four cases of arthritis deformans, and isolated organisms as follows: modified *Streptococcus viridans* thirty-two times; staphylococci five times; *Bacillus mucosus* three times; gonococci once; *Micrococcus catarrhalis* once; Welch's bacillus in fourteen cases, and diphtheroids in five cases. In some cases of deforming arthritis, he isolated the same organisms simultaneously from the fluid or capsule of the joints and the excised lymph node.

Among recent reports is that of Forkner, Shands and Poston.¹⁶ They obtained cultures in the fluid from the joint in fourteen of sixty-three cases studied. In eleven of these, the organism was *Streptococcus viridans*, in two, gonococci and in one, *Staphylococcus aureus*. In the twenty-one cases in which regional lymph nodes were cultured, the culture was positive in ten; in nine cultures the organism was *Streptococcus viridans*, and in one culture it was the gonococcus.

Cecil, Nicholls and Stainsby¹⁷ found an atypical *Streptococcus viridans* in the curetted material from the head of the femur in two cases of chronic arthritis. Cultures of the synovial membrane and lymph nodes in six cases were sterile. They were also successful in obtaining an atypical streptococcus from the blood in a rather high percentage of the cases studied.

In contrast to these observations, Crawford and Malim,¹⁸ who cultured the fluid from the joints in forty-eight cases of chronic arthritis, found the majority of the cultures to be sterile, and in a few cases from which organisms were cultured it was thought they were the results of accidental contamination.

Similarly, Richards,¹⁹ who attempted cultures of the joints in fifty-four cases of chronic synovitis, obtained *Streptococcus viridans* in only four cases. It is significant that these cultures were taken during an acute exacerbation, and an attempt was made to obtain fluid from the inflamed periarticular tissues as well as from the cavity of the joint.

15. Rosenow (footnote 1, first reference).

16. Forkner, C. E.; Shands, A. R., Jr., and Poston, M. A.: Synovial Fluid in Chronic Arthritis: Bacteriology and Cytology, Arch. Int. Med. **42**:675 (Nov.) 1928.

17. Cecil, R. L.; Nicholls, Edith E., and Stainsby, W. J.: Bacteriology of Blood and Joints in Chronic Infectious Arthritis, Proc. Soc. Exper. Biol. & Med. **26**:6, 1928.

18. Crawford and Malim, quoted by Llewellyn-Jones, R.: Arthritis Deformans; Rheumatoid Arthritis, Osteo-Arthritis and Spondylitis Deformans, New York, William Wood & Company, 1909, p. 62.

19. Richards, J. H.: Bacteriologic Studies in Chronic Arthritis and Chorea, J. Bact. **5**:511, 1920.

In 1923, Swett,²⁰ studied the synovial membrane obtained from fifteen synovectomies on eight patients suffering from chronic arthritis. These cultures were all sterile. In only one stained specimen were micro-organisms seen. Similar observations were reported by Kinsella²¹ in 100 cases of chronic arthritis: "None of these gave positive cultures as far as the joints were concerned."

The absence of any unanimity of opinion with regard to bacteriologic observations in arthritis is striking; we shall later comment on some plausible explanations for it.

MATERIAL FOR STUDY

The material used for this study came from two main groups of cases. The first comprised a series of cases in which clinical evidence of nonspecific chronic arthritis was presented. Most of these cases presented the characteristic picture of swelling in many joints, deformity and ankylosis. Clinically and at operation, these were diagnosed "chronic infectious arthritis." This corresponds to the "rheumatoid arthritis" of the British school, which is called "proliferative arthritis" according to the classification of Nicholls and Richardson, and "atrophic arthritis" by Goldthwait. The diagnosis of chronic synovitis was made in those cases in which only thickening of the synovia and periarticular structures was presented, usually with effusion of fluid into the cavity of the joint, but without demonstrable destruction of cartilage. One patient in this group, whose leg had been amputated for arteriosclerotic gangrene, had incidental arthritis of the knee with destruction of the cartilage of the femur and tibia and slight thickening of the synovial membrane. This case was of the type often designated "osteo-arthritis." The material became available for study when these patients came for reconstructive orthopedic operations, such as arthroplasty, arthrodesis and synovectomy. In some cases in which it was deemed advisable to aspirate large amounts of fluid, a section of the synovia was usually excised for pathologic and bacteriologic study.

The duration of the arthritis from the onset of symptoms was a matter of years in most cases. Thus, with the exception of four cases, in which the duration was three weeks, five months, eight months and ten months, respectively, the duration of the disease was from one to twenty years; the average was six and three-tenths years.

When pathologic examination of the excised tissues and the fluid was performed, it confirmed the clinical diagnosis of the nonspecific inflammatory nature of the arthritis.

20. Swett, P. P.: Synovectomy in Chronic Arthritis, *J. Bone & Joint Surg.* 5:110, 1923.

21. Kinsella, R. A.: Chronic Infectious Arthritis, *J. A. M. A.* 80:671 (March 10) 1923.

The second group of patients was used as controls, since this group afforded material from noninfected joints and from joints which clinically or pathologically were proved to be cases of tuberculous arthritis. The group also included two other cases: one case of old chronic osteomyelitis of the humerus with secondary involvement of the elbow, producing ankylosis, and the other, a case of old septic arthritis of the knee which had healed with resulting ankylosis.

TECHNIC

The tissues were excised at operation under aseptic precautions and were immediately taken to the laboratory for culture. Pieces of epiphyseal marrow and bone, synovial membrane, cartilage and periarticular capsule were embedded in tall tubes of dextrose-brain agar or planted in tubes of dextrose-brain broth. The reaction of the medium was adjusted to a hydrogen ion concentration of from 7.2 to 7.4. A part of the tissue, to which was added a small amount of sterile white sand and 5 cc. of dextrose-brain broth, was emulsified in a mortar under aseptic precautions. Tall tubes of dextrose-brain broth and dextrose-brain agar were then inoculated with varying amounts of these emulsions, several tubes being used as a rule for each specimen of tissue. When small quantities of synovial fluid were obtained, the entire amount of from 5 to 8 cc. was planted directly in dextrose-brain agar and dextrose-brain broth. When larger quantities were available, the fluid was centrifugated and the sediment was planted. The cultures were examined for growth at frequent intervals, over a period of from twenty-four hours to ninety days.

RESULTS

Fifteen of the twenty-five cases comprising the group of chronic infectious arthritis were classified clinically as chronic infectious arthritis, nine as chronic synovitis and one as osteo-arthritis associated with arteriosclerotic gangrene. Thirteen specimens of epiphyseal marrow and bone underlying the cartilage of the affected joints in the cases of chronic infectious arthritis were cultured. Six of these cultures were positive: two yielded indifferent streptococci; one a green-producing streptococcus, and three, diphtheroids. The remainder were sterile with the exception of an occasional tube in some series of cultures which showed a growth of *Staphylococcus albus*, apparently the result of accidental contamination. Two of eight specimens of synovial membrane obtained from the same patients were positive, one organism being a green-producing streptococcus and the other a diphtheroid. Six specimens of synovial fluid did not yield growth. One of the five specimens of synovial membrane obtained from the nine cases of chronic synovitis yielded a growth of diphtheroids. The eight specimens of synovial fluid from these patients were sterile. Two specimens of epiphyseal marrow were obtained from the knee of the patient with osteo-arthritis. One of these yielded a pure culture of indifferent streptococci. In the synovial membrane from the same joint slightly

green-producing and indifferent streptococci were found. One of the two specimens of cartilage from this joint yielded a culture of green-producing streptococci and *Staphylococcus albus*.

Thus, of the total of fifteen specimens of epiphyseal marrow and bone from various types of chronic infectious arthritis, seven were positive. Three of the organisms were indifferent streptococci, one was a green-producing streptococcus and three were diphtheroids. Of fourteen specimens of synovial membrane, four were positive; in two cultures the organisms were green-producing and indifferent streptococci, and in two, diphtheroids. One of the two specimens of cartilage yielded green-producing streptococci and *Staphylococcus albus*. The fourteen specimens of synovial fluid obtained from all these cases were sterile, except for contamination with gram-positive bacilli in two cases. In a few other instances (five specimens of epiphyseal marrow, and three specimens of synovial membrane), an occasional tube showed *Staphylococcus albus* or gram-positive bacilli which were probably the result of accidental contamination.

In contrast with these data are the results of cultures from the series of cases used as controls. Forty specimens of tissue were available for this purpose. Twenty-one of these specimens were from noninfected joints. Among these were cases of internal derangement of the knee joint, simple intracapsular fractures and old poliomyelitis in which arthrodesis was performed. Fourteen specimens were from proved cases of tuberculous arthritis; one specimen was from a case of old chronic osteomyelitis with secondary involvement of the joint, and four specimens were from a case of old septic arthritis of the knee. These forty specimens of tissue comprised epiphyseal marrow and bone, synovial membrane, synovial fluid, cartilage and the peri-articular capsule. Ten of the seventeen cultures that were positive yielded *Staphylococcus albus*, two gram-positive bacilli, two micrococci, two gram-positive bacilli and *Staphylococcus albus* and one a diphtheroid. Some of these organisms were obviously the result of contamination, but it is probable that in other instances the organisms represented secondary invaders in diseased tissue. The significant fact is that in none of these forty control specimens did we find any cultures of streptococci, and the culture of diphtheroids came from the specimen of epiphyseal marrow from the case of septic arthritis secondary to old chronic osteomyelitis. /

The streptococci that were obtained from the arthritic tissues were all streptococci in short chains (figs. 1 and 2). On blood agar none produced hemolysis. The predominating tendency was not to produce pigmentation, but in some instances the primary cultures either showed a slight greenish pigmentation or were definitely of the green-producing variety. Morphologically, the diphtheroids appeared to be midway between true diphtheroids and very short chains of fine streptococci.

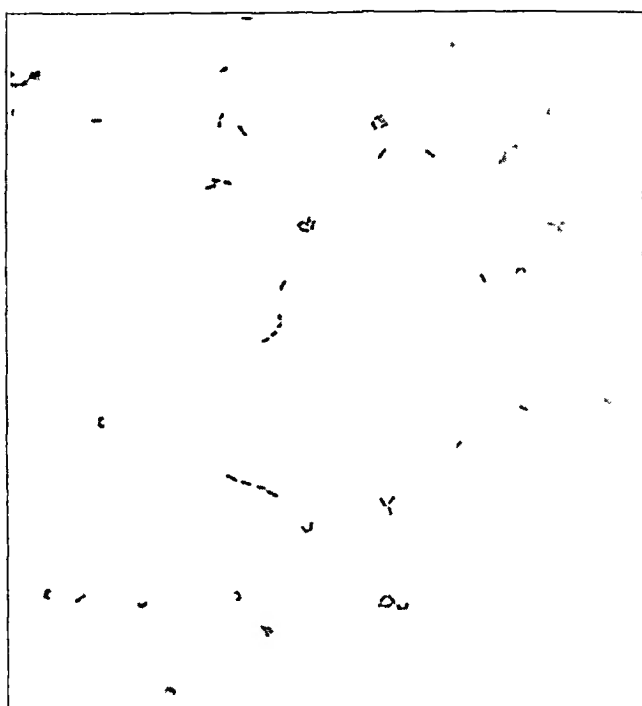


Fig. 1.—Dextrose-brain broth culture of short-chained (indifferent) streptococci from epiphyseal marrow in chronic infectious arthritis. Gram stain; \times 1,200.

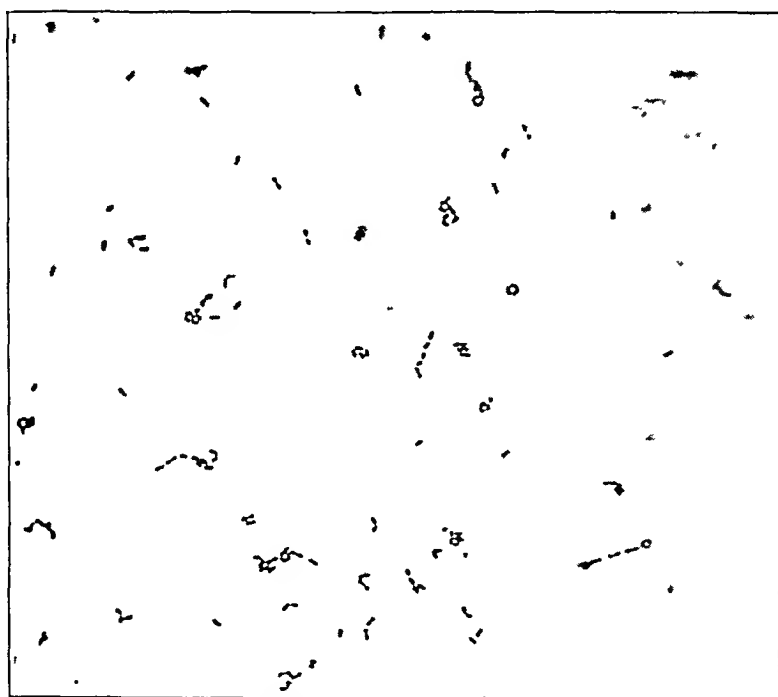


Fig. 2.—Dextrose-brain broth culture of short-chained (indifferent) streptococci from synovial membrane in chronic infectious arthritis. Gram stain; \times 1,200.

Primary cultures usually did not grow on blood agar. Repeated subcultures did not show marked variation in morphology. In view of their morphologic similarity to streptococci and the existence of mutation between certain diphtheroids and streptococci, it seems possible that the diphtheroids in arthritis may represent mutation forms of the original streptococci. However, we have no proof of this.

In order to test the elective localizing tendencies of some of the organisms isolated from arthritic tissues, four strains were injected into ten rabbits. Dextrose-brain broth cultures, approximately from eighteen to twenty-four hours old, were injected intravenously into the marginal ear vein in dosages varying from 4 to 11 cc., depending on the size of the rabbit and the density of the culture. This injection was repeated from two to four times. The rabbits were allowed to live for from four to eighty-three days. Aspiration of the joints was usually performed on the second day after the last injection. Necropsy was performed as soon as possible after death; the organs were examined for lesions, and cultures were taken from the heart's blood, joint fluid, liver and spleen.

Two strains of streptococci, one of the green-producing variety and one indifferent, obtained from the synovial membrane and one strain from the epiphyseal marrow were injected into eight rabbits. Non-purulent effusions developed in one or more joints of five, and the periarticular structures became swollen. From six of the eight rabbits, streptococci, morphologically and culturally identical with those injected, were obtained from the joint fluid, either at the time of aspiration or at necropsy (fig. 3). Of the other organs that were cultured, the heart's blood was positive in only two instances, the liver in two instances and the spleen in none. At necropsy, the affected joints showed only the residuum of the effusion or periarticular swelling. In none of the rabbits was there any destruction of the cartilage or bone, and none of the other organs showed gross lesions (fig. 4).

Histologic study of the affected joints revealed mainly edema of the synovial membrane and periarticular capsule with infiltration of round cells which were predominantly lymphocytes and large endothelial leukocytes (macrophage cells). These were scattered diffusely throughout the entire thickness of the synovia, with here and there a more dense collection of cells. There was a tendency for some of the cells to be closely aggregated about the smaller arterioles, but this relationship of the cells to the vascular channels was not at all constant nor was it a prominent feature. In animals in which the arthritis had existed for several weeks there was evidence also of proliferation of fibroblasts (figs. 5 and 6). Sections of the synovia stained by the Gram method revealed a few scattered gram-positive to gram-negative diplococci and coccus forms of varying sizes and shapes (fig. 7). In some instances the coccus forms appeared to be dividing into small



Fig. 3.—Dextrose-brain broth culture of short-chained (indifferent) streptococci from fluid of joint of rabbit into which injections of streptococci isolated from synovial membrane from cases of arthritis were made. Gram stain; \times 1,200.



Fig. 4.—Shoulder joint of rabbit into which was injected streptococci isolated from epiphyseal marrow in a case of chronic infectious arthritis; marked edema of the synovia and of the periarticular capsule without destruction of cartilage.



Fig. 5.—Synovial membrane of knee joint, showing edema and diffuse cellular infiltration; the rabbit lived thirty-seven days; $\times 75$.

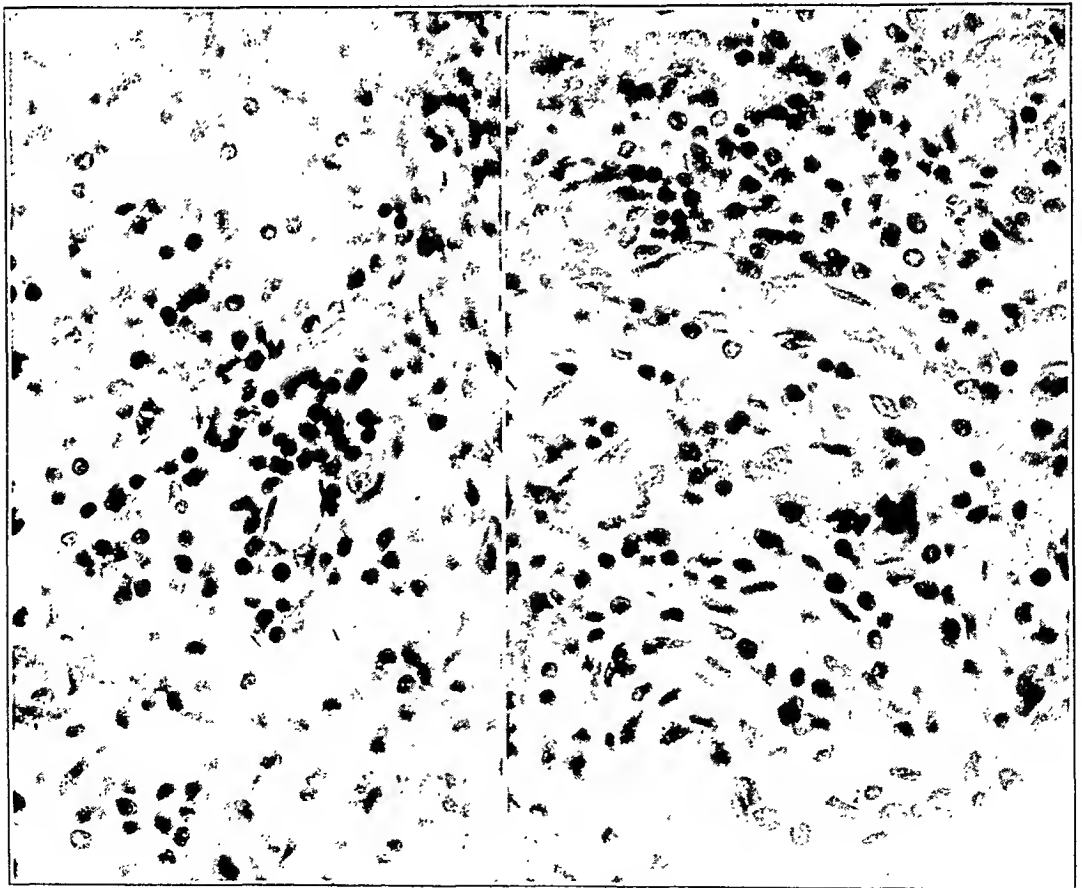


Fig. 6.—Section of synovia, showing infiltration with lymphocytes and endothelial leukocytes and beginning proliferation of fibroblasts; $\times 325$.

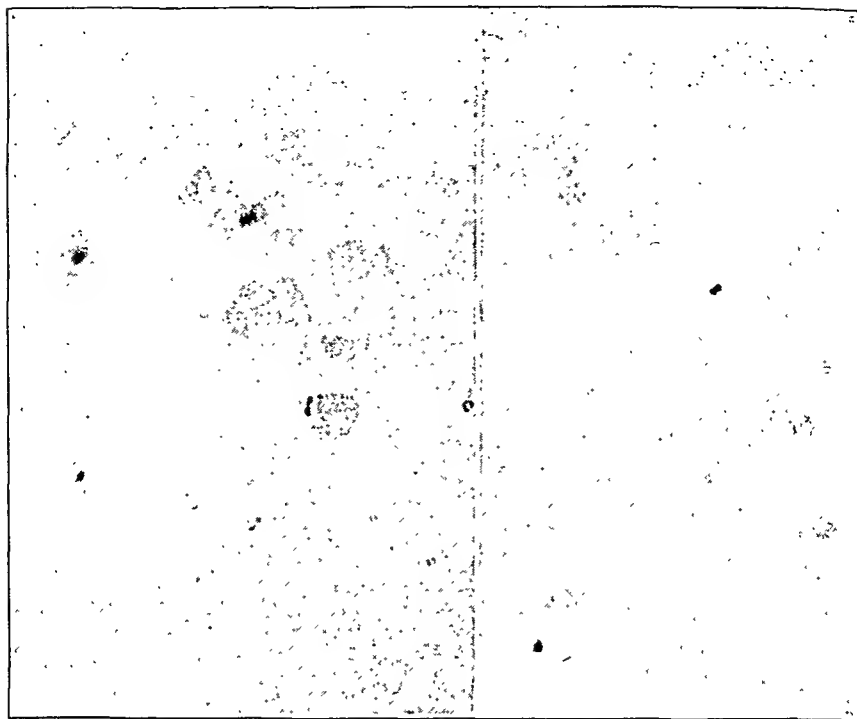


Fig. 7.—Section of synovial membrane, showing diplococci within an area of cellular infiltration. Gram stain; $\times 1,000$.

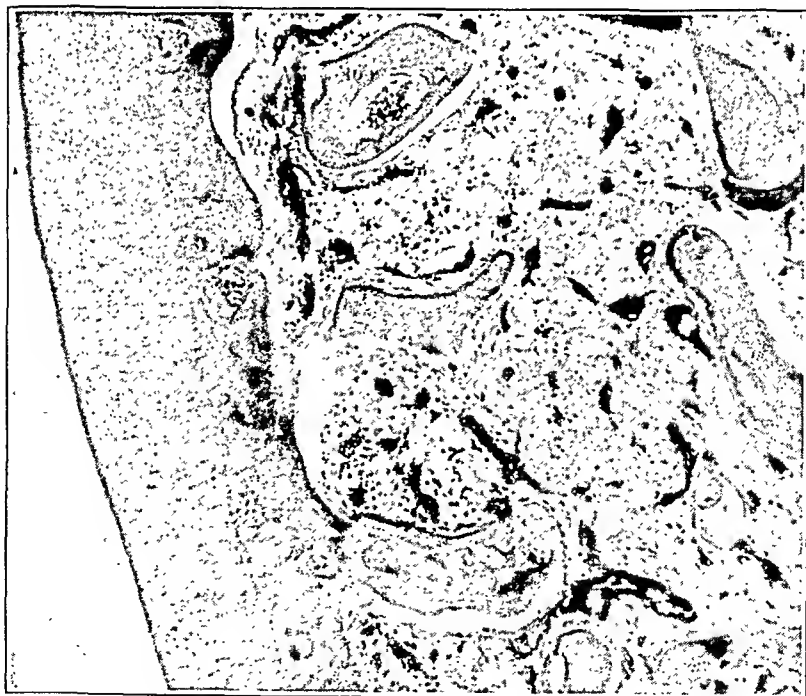


Fig. 8.—Section of femur, showing normal cartilage of knee joint and vascular congestion in the epiphyseal marrow; $\times 50$.

diplococci. These were found chiefly in the more superficial layers of the synovial membrane and within areas of cellular infiltration. Undoubtedly, diplococcus forms were seen in what appeared to be endothelial leukocytes. The cartilage was always intact and did not show degenerative changes. The marrow frequently showed marked vascular congestion (fig. 8), and occasionally it showed hyperplasia of its cellular elements. This was usually equally marked in the epiphyseal and diaphyseal marrow, although occasionally the marrow subjacent to the cartilage of the joint showed the more pronounced degree of hyperplasia. One of the diphtheroids obtained from the epiphyseal marrow in a case of arthritis was injected into two rabbits. In neither of these did arthritis or lesions in other organs develop. Neither could we recover the organism on culture.

COMMENT

In general, our results are in agreement with those previously reported by others, since we were able to culture bacteria from a limited percentage of arthritic tissues. It is evident also that the organism can be isolated more often from the bone-marrow of the epiphyses adjacent to affected joints than from the synovial membrane. On the contrary, our attempts to isolate bacteria from the synovial fluid were entirely unsuccessful; this is in consonance with the observations of Swett, Kinsella, and Cecil, Nicholls and Stainsby, but differs from those of Forkner, Shands and Poston. Moreover, the organisms obtained were either streptococci or diphtheroids. Within the streptococcus group, which had a distinct tendency to localize in the joints of rabbits, slight cultural variations occurred. These differences were recognizable only by the variable degree of production of pigment on blood agar, but this is not indicative of any great degree of heterogeneity. Swift, Derick and Hitchcock²² occasionally isolated two distinct strains of streptococci from the same patient suffering from rheumatic fever at different times, and in one instance two types from one group of subcutaneous rheumatic nodules removed at biopsy.

Several significant questions occur for consideration: Is there any etiologic relationship of the bacteria isolated from arthritic tissues to the disease process? What is the explanation for the relative infrequency with which organisms can be isolated from arthritic tissues? Is this compatible with an infectious etiology of chronic arthritis? How can we reconcile the wide divergence in the percentage of positive cultures and the multiplicity of bacterial strains reported by different observers? What particular significance may be attached to the presence

22. Swift, H. F.; Derick, C. L., and Hitchcock, C. H.: Bacterial Allergy (Hyperergy) to Nonhemolytic Streptococci in Its Relation to Rheumatic Fever, *J. A. M. A.* **90**:906 (March 24) 1928.

of the bacteria in the epiphyseal marrow and synovial membrane and their absence from the synovial fluid?

Proof of the etiologic significance of bacteria isolated from arthritic tissues has not always been available, owing to the extreme difficulty of reproducing chronic progressive arthritis in experimental animals. This fact suggests that in man some other factors, as yet unknown, play a large part in predisposing to infection, or in initiating a process in which infection eventually assumes a dominant part. This is exemplified by one of our cases of static arthritis of the foot in which there developed subsequently the typical pathologic picture of infectious arthritis and from which we isolated a green-producing streptococcus. The nearest approach, then, to the identification of the causative organisms is by a study of their elective localizing tendencies when injected into experimental animals. In this manner we were able to show that all of these strains of streptococci gave evidence of localization in one or more joints of most of the rabbits into which injections were made. We cannot be certain of the significance of the diphtheroids that we isolated from arthritic tissues. One of these organisms did not show any tendency to localize in the joints of the rabbits. We are aware also of the caution which must be exercised in attributing pathogenic significance to them. Nevertheless, they cannot be entirely disregarded. From our knowledge of the "pleomorphism" and of the tendencies to dissociation among the streptococci and diphtheroids, it seems possible that these diphtheroids represent mutation forms of the original streptococci.

On analysis of our data, it does not seem surprising that positive cultures are obtained with such relative infrequency. As we have indicated, the average duration of the symptoms in the cases of arthritis was a matter of many years. The operations were usually performed to correct the result of ankylosis. In all cases, absolute quiescence of the process was assumed before they were deemed suitable for such operations. Even those patients who presented hydrops of the joints had usually had the effusion for a period of months before coming to operation. It would seem, then, that the organisms we obtained were only those which retained their viability despite the natural reparative processes which had been exerted by the affected tissues over periods of months or years.

It is clear that the absence of bacteria in cultures of arthritic tissues, at the time when such material becomes available to us for study, cannot be construed as proof of the noninfectious nature of the disease. On the other hand, the finding of positive cultures, even in a small percentage of cases, is strongly suggestive of its infectious etiology. It is unfortunate that circumstances do not permit of bacteriologic cultures of arthritic tissues, particularly of the epiphyseal marrow, during the early, active stages of the disease.

Of the bacteria that have been isolated from tissues in chronic arthritis, the nonhemolytic (green-producing and indifferent) streptococci have been shown to play the most prominent part. The report of Rosenow,¹⁵ and the reports of Billings, Coleman and Hibbs, Forkner, Shands and Poston, Cecil, Nicholls and Stansby, and Richards show that these streptococci are found either exclusively or, at least, most frequently. Our own observations are in agreement with this for, excluding the occasional *Staphylococcus albus* that was found in control cultures as well as in the arthritic tissues and, therefore, may be assumed to be either a secondary invader or a contamination, the arthritic tissues yielded only nonhemolytic streptococci and diphtheroids. Yet one cannot dismiss the observations of Schüller and Crowe who have consistently found other organisms in arthritic tissues. In the absence of final proof of the etiologic relationship of any of the organisms that have been reported, we must conclude tentatively that various types of bacteria may be causative in chronic arthritis. That the apparent similarity of pathologic pictures must not imply bacteriologic unity of the etiologic agent is based on fact. Specific arthritis, which is frequently associated with bacillary dysentery and infection by *Brucella abortus*, is similar in its clinical manifestations, but it has widely different causative organisms. The predominance of the streptococci among our positive cultures, and among those reported by others, indicates that these organisms probably are of first importance from an etiologic standpoint in chronic infectious arthritis.

The relative frequency with which bacteria can be cultured from the epiphyseal bone and marrow subjacent to arthritic joints seems to us of considerable significance. Whether the infection in the subchondral marrow is the primary one and what its relation is to the general pathologic process in the joint are not clear. The pathologic studies of Milne²³ support the hypothesis of primary epiphysitis in the pathogenesis of many cases of chronic arthritis. Recent studies by Ryneerson²⁴ on the fate of dyes injected into the cavity of the joint suggest one possible means of epiphyseal infection in arthritis. He has shown that absorption of dyes from the synovial sac occurs readily and that large macrophages laden with phagocytosed foreign material eventually reach the reticulo-endothelial system, of which the marrow is the most extensive part. It is conceivable, therefore, that many of the bacteria that attack primarily the various structures in and about the joint eventually find their way to the reticulo-endothelial system where secondary foci may be established. Similarly, we may explain the absence of bacteria in the fluid of the joint in long-standing cases

23. Milne, L. S.: Chronic Arthritis, *J. Path. & Bact.* **16**:199, 1911.

24. Ryneerson, E. H.: Studies on the Physiology of Joints: Mechanism of Absorption of Various Substances from Synovial Cavity, *Proc. Staff Meet., Mayo Clin.* **3**:171, 1928.

of arthritis by the phagocytic action of the cellular elements in the fluid. The potency of such phagocytosed bacteria to establish secondary infectious foci in the marrow is, however, unknown. Neither do we have conclusive data as to the part played by primary epiphyseal foci of infection in the pathogenesis of chronic arthritis. It is certain, however, that too little attention has been given in the past to bacteriologic studies of the epiphyseal marrow subjacent to arthritic joints. There is, it is true, a paucity of such material which is available for study. Nevertheless, it would seem that relentless study of this problem may yield data of considerable importance to our understanding of chronic arthritis.

SUMMARY AND CONCLUSIONS

1. Nonhemolytic streptococci were isolated from the epiphyseal marrow and bone, from the synovial membrane and from the cartilage obtained from joints affected with chronic nonspecific arthritis.

2. The synovial fluid from these cases did not yield organisms other than those from occasional contamination.

3. The epiphyseal marrow and bone yielded bacteria more frequently than any of the other tissues. This may indicate a significant site of infection in the pathogenesis of arthritis which has not been given sufficient consideration in the past.

4. Cultures of control tissues from joints other than those of nonspecific arthritis yielded organisms other than streptococci. These could be ascribed either to secondary infection or to accidental contamination.

5. Several of the streptococci isolated from arthritic tissues showed marked elective affinity for joints when injected intravenously into rabbits. One diphtheroid which was similarly injected did not localize in the joint.

6. The relative infrequency with which organisms were grown from arthritic tissues is probably due to the long duration or inactivity of the disease when the material became available for study.

7. The negative cultures from tissues of the joints are not proof of the noninfectious nature of the disease; the presence of bacteria, even in a small percentage of cases, is strongly suggestive of infection in the etiology of chronic arthritis.

8. The nonhemolytic green-producing and indifferent streptococci seem to be of first etiologic significance in chronic arthritis, in confirmation of the previous work of Rosenow²⁵ and others.²⁶

25. Rosenow, E. C.: *The Etiology of Articular and Muscular Rheumatism*, J. A. M. A. **60**:1223 (April 19) 1913; *Studies in Elective Localization: Focal Infection with Special Reference to Oral Sepsis*, J. Dent. Research **1**:205, 1919.

26. Meisser and Brock (footnote 2, first reference). Nakamura (footnote 2, second reference). Nickel (footnote 2, third reference). Poynton and Paine (footnote 10). Billings (footnote 12). Forkner, Shands and Poston (footnote 16). Cecil, Nicholls and Stainsby (footnote 17). Richards (footnote 19).

LIPOID NEPHROSIS

PATHOLOGY, GENESIS AND RELATION TO AMYLOIDOSIS *

PHILLIP F. SHAPIRO, M.D.

CHICAGO

As numerous as are the articles and discussions on lipoid nephrosis, so rare are the actual cases anatomically proved and reported. Few subjects in medicine have enjoyed as much speculation on as little material support or suffered as much the consequence of confusion. Of the small number of cases clinically considered, few are checked by autopsy for the excellent reason that usually the patients do not die. The great majority of those which are so checked, prove, contrary to the best supported clinical diagnoses, to be only glomerulonephritis with a nephrotic component (einschlag). Many others are so tangled up with amyloidosis that they are ordinarily ruled out of argument. The specific renal tubule damage in pregnancy and in various infections and intoxications account for still other pretenders.

Aschoff finally denied altogether the existence of a genuine lipoid nephrosis. Wells¹ stated that he had looked all his life for a pure case in an adult. He had many clinically classic cases of nephrosis in which at autopsy the gross anatomic picture was just as classic of nephrosis, but microscopically he always found, to his disappointment, a subacute or chronic glomerulonephritis. Loehlein² and Elwyn³ insisted that all the cases of so-called primary lipoid nephrosis are in reality primarily glomerulonephritides, no matter how the inflammatory is later obscured by the nephrotic element. Even those who do admit the reality of lipoid nephrosis, hesitate, as does Herxheimer, at the possibility of nephrotic contracted kidneys. Klemperer⁴ affirmed that he had never believed in lipoid nephrosis until he had seen for himself a true case. Subsequently, he even found one with nephrotic contraction. Nephrosis may be counterfeited so closely by other conditions that no cautious pathol-

* Submitted for publication, Nov. 23, 1929.

* From the Department of Pathology of the Cook County Hospital.

1. Wells, H. G.: Discussion of Bell, L.: Lipoidnephrosis, read at meeting of Am. A. Pathologists & Bacteriologists, Chicago, 1929, Am. J. Path. **6**:541 (July) 1929.

2. Loehlein, M.: Ueber Fettinfiltration und fettige Degeneration der Niere des Menschen, Virchows Arch. f. path. Anat. **180**:1, 1905.

3. Elwyn, H.: Nephritis, New York, The Macmillan Company, 1926; The Pathogenesis of Lipoid Nephrosis, Arch. Int. Med. **38**:346 (Sept.) 1928.

4. Klemperer, Paul, in discussion of Kohn, J.: Lipoid Nephrosis, Tr. New York Path. Soc. Arch. Path. **6**:528 (Sept.) 1928.

ogist, unless it has been his rare good fortune to see one of the few anatomically established cases, will accept it as an entity.

Yet from time to time cases are reported which even the firmest skeptic cannot deny. Among these may be mentioned those of Munk,⁵ Volhard,⁶ Fahr,⁷ Loewenthal,⁸ Kaufmann,⁹ Kohn,¹⁰ Murphy,¹¹ Cabot¹² and Rachmilewitz.¹³ Cases of nephrotic contracted kidneys are even more rare. Yet irrefutable ones have been described by Volhard, Munk, Kaufmann, Bohnenkamp and Bergstrand. Almost all of them occurred in syphilitic patients. That lipid nephrosis, though rare, may indeed occur without any demonstrable nephritis and distinct from amyloidosis and that independently it may be a cause of death was demonstrated by an unusual series of autopsy material which I had the opportunity to study.

This material also served to recall attention to the many pitfalls of the clinical diagnosis. It is known, in particular, that cases of chronic nephritis with a nephrotic component can reproduce accurately every chemical and clinical detail of a pure nephrosis. Amyloidosis may be buried out of view under the syndrome of lipid nephrosis or, on the other hand, may completely overshadow it. The clinician is obliged to venture his rare diagnosis of nephrosis with great caution and reserve. Accordingly, the opportunity was also taken to try out a clinical test which though not widely known in this country has been used considerably abroad to help somewhat to alleviate these diagnostic difficulties.

5. Munk, F.: *Pathologie und Klinik der Nierenerkrankungen*, Berlin, Urban & Schwarzenberg, 1925; *Zur Pathogenese der nephrotischen Schrumpfniere*, *Virchows Arch. f. path. Anat.* **226**:81, 1919.

6. Volhard, F., and Fahr, T.: *Die Brightische Nierenkrankheit*, Berlin, Julius Springer, 1914.

7. Fahr, Thomas: *Pathologische Anatomie des Morbus brightii*, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, vol. 6, p. 172.

8. Loewenthal, Karl: *Weitere Beiträge zur Frage der Lipoidnephrose*, *Virchows Arch. f. path. Anat.* **261**:109, 1926; *Weitere Beiträge zur Frage der Lipoidnephrose*, *Beitr. z. path. Anat. u. z. allg. Path.* **79**:497, 1928.

9. Kaufmann, J., and Mason, E.: *Nephrosis*, *Arch. Int. Med.* **35**:561 (May) 1925.

10. Kohn, J.: *Lipoid Nephrosis*, *Arch. Path.* **6**:528 (Sept.) 1928.

11. Murphy, F. D., and Warfield, L. M.: *Lipoid Nephrosis*, *Arch. Int. Med.* **38**:449 (Oct.) 1926.

12. Cabot, R.: *Fatal Albuminuria without Nephritis*, *New England J. Med.* **199**:97, 1928.

13. Rachmilewitz, M.: *Hypercholesterolemia Associated with Hepatosplenomegaly and Nephrosis*, *J. A. M. A.* **93**:604 (Aug. 24) 1929.

PURE LIPOID NEPHROSIS

CASE 1.—*History*.—A colored boy, 3 years old, was brought to the Cook County Hospital in August, 1928, suffering from a severe generalized edema. He was discharged in January, 1929, as improved. The boy was tolerably well until April, 1929, when puffiness about the eyes began, and he was readmitted to the hospital.

He had been born after a normal delivery at full term. He was breast fed; cod liver oil and orange juice had been given. His development was normal. Chickenpox had been his only ailment before the edema began. The mother was 29 years old, living and well; she had borne 3 children, with no miscarriages.

Physical Examination.—The results of physical examination were negative, except for the puffiness about the eyes. No other complaints or observations were registered. The facial edema gradually increased and spread until, within two weeks after entrance, it was severe and involved the entire body. The pharynx showed a slight injection, and the temperature varied from normal to 101 F.

Laboratory Observations.—Doubly refractile lipid droplets were found in the urine. The albuminuria was severe, with many finely granular casts but no red blood cells. The erythrocyte count was normal, 5,200,000; the leukocyte count, 9,650 per cubic millimeter.

The report on the blood chemistry was as follows: Urea nitrogen amounted to 13.6 mg. per hundred cubic centimeters. The cholesterol was elevated to 416 mg. There was a reversed albumin-globulin ratio. Serum albumin was decreased to 1.64 per cent as compared with a normal range of from 4.6 to 6.7 per cent.¹⁴ The serum globulin was at the high level of 2.3 per cent as compared with the normal variation of from 1.2 to 2.3 per cent.

Clinical Diagnosis.—The diagnosis was nephrosis and pharyngitis.

Treatment and Course.—The child was placed on a diet high in protein, and for three days given ammonium chloride, 5 grains (0.3 Gm.) three times a day. On April 27, he was given 0.25 cc. of sodium mercurisalicylallylamido acetate (solyrgon) intravenously. The edema continued to increase, and three days later, on April 30, a second dose was given. He died unexpectedly several hours after the second injection.

Postmortem Examination.—The marked puffiness of the face, especially of the eyelids, the moderate pitting edema over the entire trunk and the severe edema of the genitalia were striking observations. The lips were pale. The abdomen was distended; its cavity contained 400 cc. of a chyliform fluid. Each pleural cavity contained 100 cc. of similar fluid.

The heart was of normal weight, 68 Gm. The wall of the left ventricle was 10 mm. thick; that of the right, 2 mm. thick. The myocardium was pale and soft. The lungs were moist with foamy fluid. The liver was enlarged to 690 Gm., and was pale and moist. The spleen weighed 68 Gm. and was firm; its corpuscles were enlarged. The lymph nodes of the abdominal cavity were enlarged and waterlogged.

The kidneys were enlarged, and together weighed 200 Gm. as compared with the normal, at that age, of 100 Gm. The capsule stripped easily, leaving a smooth, pale gray surface. On surfaces made by section, the cortex was 8 mm.

14. Myers, V. C.: Chemical Changes in the Blood and Their Clinical Significance, *Physiol. Rev.* 4:279, 1924.

wide, pale gray with opaque, yellowish-white patches and lines, radiating toward the pelvis. The medulla was deeper gray and sharply differentiated from the cortex.

Microscopic Examination.—The glomeruli of the kidney were normal in size, number and distribution, with unchanged cellularity and tufts moderately filled with blood. Many of the Bowman spaces were narrow and empty. Others were wide and filled with a homogeneous pink material containing a few fine lipid

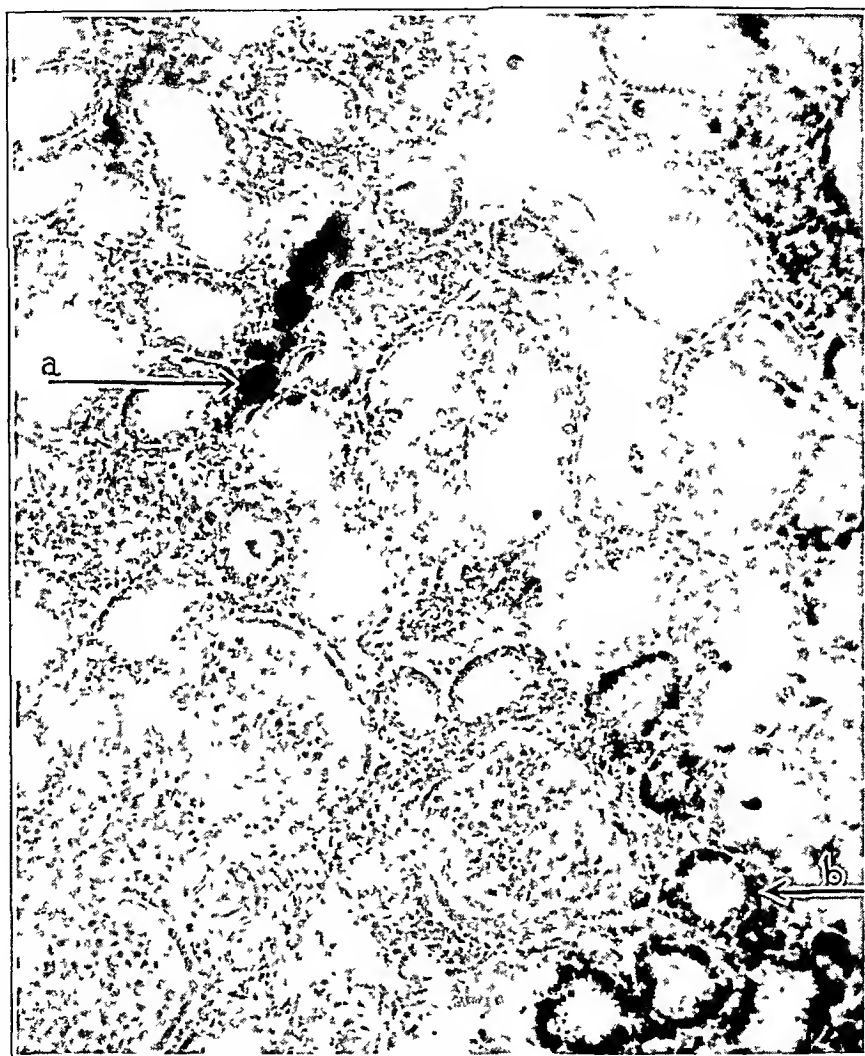


Fig. 1.—Kidney showing extensive lipid infiltration in single proliferated sessile histiocytes of the interstitial tissue and in groups of them (*a*), and in the convoluted tubuli of the first order (*b*). The capsular epithelium of the glomeruli is somewhat swollen, but the glomeruli are intact. Sudan III; hematoxylin; $\times 150$.

granules. The parietal lining of the capsules was moderately swollen and bulged into the spaces. Fine fat droplets were scattered through its cells, as well as through those of the visceral glomerular epithelium.

Groups of convoluted tubuli arranged closely about the glomeruli showed a large amount of fat in their lining epithelium. This fat, which was doubly

refracting, had accumulated mostly near the base of the cells. The cells were enlarged, so that the lumen of these convoluted tubuli of the first order was narrow. Their cytoplasm was oxyphilic and granular, but had no hyaline droplets. The nuclei were well preserved, enlarged, with well defined chromatin structure. An occasional fat-filled cell and homogeneous pink cast was found free in the lumen of these tubules.

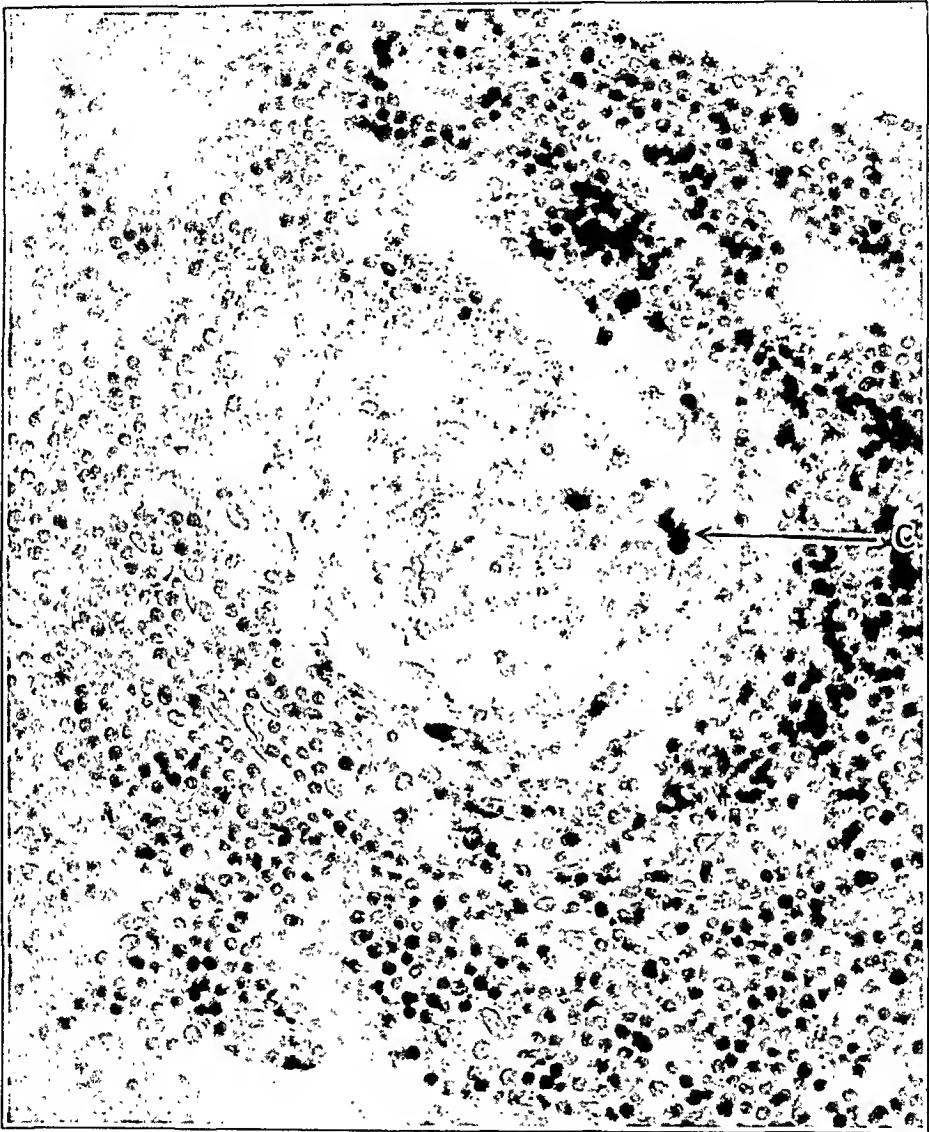


Fig. 2.—Lymph node; germinal follicle with swollen and proliferated reticulum cells containing fine lipoid granules. Sudan III; hematoxylin; $\times 300$.

The other convoluted tubules and the ascending limbs of Henle's loops showed but slight fat, and no epithelial enlargement. The collecting tubules and the descending limbs of Henle's loops were unchanged, except for the granular and homogeneous casts in their lumen.

The interstitial tissue was somewhat edematous, separating the tubules by small, loose spaces. Especially in the deeper layers of the cortex, it contained many large, oval or branched cells with an ample cytoplasm and deeply stained nuclei. These cells were loaded with fat which gave a brilliant double refrac-

tion. The vessels were unchanged, except for a small amount of fat scattered in the intima and adventitia of the smaller arteries.

In the liver, the Kupffer cells were stuffed with lipid granules which filled their branches. There was a little fat in the liver cells. It was not doubly refractile.

The follicles of the spleen contained distinct, lightly stained centers. They were composed of elliptical and fusiform cells with pale-stained, oval nuclei. The cytoplasm of these cells contained fine and medium-sized lipid granules, which were doubly refracting. Between these cells there were a few lymphoblasts which did not contain fat. The endothelium of the sinuses appeared slightly swollen, and in places contained fine, dustlike lipid granules.

In the mesenteric lymph nodes, the centers of the cortical follicles were composed of elongated, swollen or branched cells which were filled with lipid droplets. The sinuses were wide; their lining was swollen and showed a fine lipid infiltration.

In the alveolar spaces of the lung were narrow, elongated cells, adjacent to the capillaries. They contained small fat droplets. Single large round cells with fat droplets were seen free in the alveolar spaces.

All layers of the cortex of the suprarenal glands were rich in lipid material. There were single small fat droplets in the cells of the medulla.

The reticulum cells of the thymus were filled with lipid droplets. The plasma in the vessels even stained a light orange yellow with sudan III.

Anatomic Diagnosis: The anatomic diagnosis was: lipid nephrosis; generalized anasarca; chylous ascites and bilateral hydrothorax; diffuse edema of the lungs; edema of the liver; hyperplasia of the lymph nodes, and of the lymph follicles of the spleen, and parenchymatous degeneration of the myocardium.

Comment.—Pure lipid nephrosis does exist. The case just described cannot summarily be dismissed as a form of nephritis. As long as one can muster any appreciable inflammatory changes, it may be conceded Elwyn and his school that the nephrosis is only a secondary component to a slight but healed nephritis. But when, in cases such as this, the most exhaustive search fails to reveal the slightest evidence of renal inflammation, one is left without anatomic support for such a theory.

In nephritis, with a well established glomerular damage, some tubular injury is expected. But when the tubular and interstitial changes appear in a severity out of all proportion to the insignificant or totally absent glomerular ones, the histologic picture loses all resemblance to nephritis, and from it these cases must be sharply separated. Even if some glomerular changes are noted, such as the swelling of the parietal epithelium of Bowman's capsule and the lipid infiltration of the glomerular tufts, they bespeak a degenerative rather than an inflammatory process. They can be ranked only as the glomerulonephrosis which accompanies the overwhelming tubulonephrosis. Even if an occasional glomerulus should be found with a definite inflammatory reaction, with increased cellularity, infiltrations and decreased blood content of the tufts, one would still have no right to charge the whole histologic

picture to a nephritis. For this trifling inflammatory change might just as well be only an incidental complication, secondarily engrafted on a well defined, chronic lipid nephrosis. Furthermore, this slight glomerulitis could never account for the widespread tubular and interstitial damage. It is this disparity which forces one to recognize in such cases the independence from nephritis of a pure lipid nephrosis.

Nephrosis is grouped with the renal diseases, yet the kidneys are only byways in its pathogenesis. Fundamental in its genesis is some disturbance in lipid-protein metabolism. The cause of this disturbance is, to present knowledge, uncertain. In children, an infectious process in the upper part of the respiratory tract, such as occurred in my case, is generally inculcated. A history of numerous infections is often obtained in cases of nephrosis, but no more frequently than in cases of other diseases. It is to be expected that infections will crop up incidentally in the history of any chronic ailment. Munk stressed the importance of syphilis. Cases appear frequently with tuberculosis, but are often then mixed with amyloidosis. Various endogenous and exogenous intoxications, anaphylaxis, endocrine disturbance, constitutional predisposition have all been invoked, but none proved. It has been set up as one of the diseases of the reticulo-endothelial system, but its histologic aspects and clinical picture bear only vague resemblance to them. It differs as widely also from the pictures of lipemia in cholemia and diabetes.

Be its cause what it may, nephrosis is a special type of disturbance of lipid-protein metabolism, just as diabetes mellitus is a specific disturbance of carbohydrate metabolism. This analogy led Epstein¹⁵ to suggest as a substitute for "nephrosis," the term "diabetes lipoproteinicus." "Lipoid-protein diabetes" is a better term than "nephrosis," for it directs attention more properly to the generalized disturbance. The kidneys assume prominence only because they are heavily involved in their rôle as excretory organs for the products of disturbed metabolism. Secondarily, they are damaged, but nephrosis is primarily not a disease of the kidney.

Indeed, the rôle of the liver is coming to be regarded as of greater consequence than that of the kidney. That a definite damage of the liver exists is indicated by Knauer's¹⁶ observation in nephrotic children of a symptomless but definite hypoglycemia. The loss of trypanocidal activity by the blood serum in nephrosis, as well as the general water imbalance, also confirms the assumption of a liver deficiency, for the

15. Epstein, A.: Ueber Diabetes albuminuricus, die sogenannte chronische Nephrose, Arch. Verdauungskr. **44**:31, 1928.

16. Knauer, Hans: Neue Berunde bei der Lipoidnephrose, Klin. Wchnschr. **7**:987, 1928; Ist die Nephrose eine Nierenerkrankung? Med. Klin. **23**:862, 1927.

liver is normally active in these functions. As anatomic evidence, one can cite only the extensive fatty changes found.

Whatever is its cause or its line of attack, the generalized cellular damage with its disturbance of lipid-protein metabolism leads to a profound alteration in the chemistry of the body tissues and fluids. There is a massive albuminuria with a marked decrease in the albumin content of the blood serum. The albumin in the urine is not simply that which has been lost from the blood.

The loss is far too large to be so accounted for. Nor does it come from the food, for feeding huge quantities of protein does not aggravate it. The albuminuria is endogenous, not exogenous. It is derived from the breaking down of cells, from the altered protein metabolism all over the body and especially, according to Andrews,¹⁷ from the liver.

This albumin would pile up in the blood were it not so readily able to pass through the kidneys. Munk considered the kidneys to be permeable to it because it is an abnormal, an altered albumin. By passing an electric current through serum, he found a shift of its proteins toward a euglobulinemia. When he then perfused it through a dog's kidney, he obtained an albuminuria, and a marked reduction in the albumin content of the serum. The globulin content remains normal because this protein has larger molecules which cannot pass through. It may even rise as a result of the cellular disintegration and the shift of proteins described by Munk. The globulin content may thus come to exceed the much diminished albumin, and there is a reversal of the normal albumin-globulin ratio.

In like manner, the generalized disturbance in cellular lipid metabolism unloads a large quantity of fats, particularly cholesterol into the serum. This cholesterolemia, too, is not exogenous but endogenous. For huge quantities of cholesterol may be fed without yielding the slightest rise in the cholesterolemia. The excessive cholesterol in the blood comes from the damaged cells all over the body. Buerger¹⁸ regarded it as a different kind of cholesterol from that which is seen in the lipemias of early starvation or pregnancy or narcosis or diabetes or cholemia. He distinguished that of nephrosis as an abnormal, a cytolytic cholesterolemia.

Normally, any excess of cholesterol is excreted partly by the skin, but mostly by the liver through the gallbladder and intestinal tract. For a time, the liver may be adequate in its discharge of the excessive cholesterol, but if it is damaged or if it is exhausted by this undue strain,

17. Andrews, E., and Thomas, W. A.: Origin of Urinary Proteins, *J. A. M. A.* **90**:539 (Feb. 18) 1928.

18. Buerger, Max: Der Cholesterinhaushalt beim Menschen, *Ergebn. d. inn. Med. u. Kinderh.* **34**:661, 1928.

lipoid piles up in the blood, and the serum becomes milky with it. The serum of a diabetic or cholemic patient may be rich in fat, yet none appears in the urine. A lipoidemia appears in early starvation, yet normally only slight traces of cholesterol pass through the kidney (Gardner¹⁹). The abnormal, cytolytic cholesterol of nephrosis, as compared with the retention cholesterol of cholemia, the transport cholesterol of starvation, etc., can, however, more readily pass through the kidneys and does so in huge quantities. In analogy, I mention that the bilirubin of obstructive jaundice is chemically the same as the bilirubin of hemolytic jaundice, yet the former can pass through the kidneys while the latter cannot. A massive lipoiduria follows, and doubly refractile cholesterol crystals are found in the urine.

On the kidneys, then, is thrown the chief load of evacuating the abnormal lipoids and protein. Because of its status as the pathway of excretion, a series of renal changes is secondarily induced. Four stages are herein distinguished: (1) infiltration, (2) degeneration, (3) interstitial tissue changes and (4) contraction.

At first there is only a hyperactivity of the renal epithelium cells. Their nuclei are large, with well preserved chromatin structure. Their cytoplasm is enlarged, filled with granules and droplets, stuffed with isotropic and anisotropic lipoids. They are "congested with the traffic of excretion." This affects, chiefly, the proximal convoluted tubuli of the first order, those closely grouped about the glomeruli. But it also appears in the parietal layer of the glomerular epithelium, within the glomerular tufts, and in traces through the whole remaining length of the renal units up to the collecting tubules.

This diffuse glomerulonephrosis and tubulonephrosis with heaviest involvement of the first tubular convolutions is in early stages only infiltrative. There is no evidence of degeneration. Later, as the cells become exhausted by this functional strain, they atrophy. A secondary tubular damage ensues. The nuclei become pyknotic, the cytoplasm hyalinized. Desquamated cells are seen in the lumen of the tubules, and atrophied cells in their walls. If the damage is not too great, active regeneration is seen in the tubular epithelium. Thus ends the second stage.

The glomeruli are all this time microscopically unchanged. The cholesterol in the urine is not simply that which comes from the renal tubular degeneration. The substance of all the renal tubules together could produce only a small part of the cholesterol found in the urine. Tubular degeneration just as far advanced is seen in other conditions, such as the acute infections or diabetes, without a trace of lipid appear-

19. Gardner, J., and Gainsborough, H.: Determination of Cholesterol and Cholesterol Esters in Urine, *Biochem. J.* **19**:667, 1925.

ing in the urine. The cholesterol in the urine can therefore be only partly that which is in the degenerated tubular epithelium; it comes mostly from the blood. The cholesterolemia, in turn, is derived from the disturbed metabolism all over the body.

Not every lipid infiltration or degeneration of the kidney is lipid nephrosis. These changes are seen as well after experimental adrenalectomy (MacMahon,²⁰ Gunn²¹), in the lipemia of diabetes, in acute infections, in cholemia and in chronic nephritis without a nephrotic component. The tubular cells may be filled with lipid. Singly and doubly refractile fat may be abundant in the glomerular parietal epithelium and in the tufts. Fat may even render the blood serum and the contents of the Bowman's spaces light orange in the sudan III stain. But fat changes are not "nephrosis," until the third series of changes is demonstrated.

The most characteristic change in the kidney in nephrosis is the reaction of the interstitial tissue. The sessile histiocytes of the stroma proliferate. They draw in their branches, swell up and become packed with singly and doubly refractile lipoids. This was the most prominent feature in the sections stained with sudan III of my first case. Rachmilewitz¹³ and Murphy¹¹ found the same changes. Stoerk believed that they arise through the absorption by the reticulum and endothelial cells, of the remains of the few tubular epithelium cells which from time to time disintegrate. The fat-laden, proliferated groups of histiocytes are the refuse heaps of the slow and remittent epithelial cell exhaustion. This is the most definite, positive histologic criterion of nephrosis.

All over the body, the cells of the reticulo-endothelial system participate in the burden of lipid disposal. In the lymph nodes, the reticulum cells of the follicles are packed with singly and doubly refractile lipoids. The Kupffer cells of the liver, the interstitial cells of the lung parenchyma, the reticulum cells of the spleen are similarly affected. The interstitial cells of the kidneys share in this process. Just such changes are seen also in any of the diseases of the reticulo-endothelial system, such as Niemann-Pick's disease. But in these alone, the interstitial renal changes are slight. It is when to them are added the interstitial cell proliferation and infiltration of lipid from the exhausted tubular cells that there is truly a nephrosis.

In only one condition other than true lipid nephrosis can such marked renal interstitial fatty changes be found. This is chronic nephritis with a nephrotic component. But here the presence of inflammatory

20. MacMahon, H. E., and Zwemer, R. L.: Pathologic Histology of Adrenalectomized Cats, *Am. J. Path.* **5**:491 (Sept.) 1929.

21. Gunn, F. D.; Cori, C. F., and Hartman, F. A.: Lipoid Nephrosis in Adrenalectomized Rats and Guinea-Pigs, *Proc. Soc. Exper. Biol.* **25**:410, 1928.

glomerular changes and the absence of the gross disproportion between the glomerular and tubular damage would establish its differentiation from lipid nephrosis.

With all these changes described, even to the end of the third stage, renal function is still well maintained (Holmes²²). There is no hematuria, no anemia, no retinitis, no high blood pressure, no cardiac hypertrophy. The phenolsulphonphthalein test is normal, and there is no azotemia even on a diet high in protein. Only in the stage of active edema is there retention of water and salt. The Aldrich test injection is then rapidly absorbed.²³ The Mosenthal test shows good power of urine concentration, but a delayed excretion of ingested fluids. Diuretics fail to act until the edema of itself begins to subside.

For the edema is extrarenal (Fanconi²⁴). It is not a result of inability of the kidneys to excrete water (Koranyi²⁵). If it were, there would be a hydremia in nephrosis. Actually, the blood is thicker than normal in nephrosis, so that hemoglobin and red blood cell counts may be excessive. The edema is a result of water retention by the tissues. The kidneys would well be able to excrete this water, if the fluid-soaked tissues would only release it.

The desperate clinical attempts to relieve the edema meet, therefore, with variable success. Among those tried may be mentioned a diet high in protein and low in fat, restriction of water and salt, thyroid therapy (Epstein²⁶), antisyphilitic treatment in syphilitic cases, and the use of calcium, parathyroid (Lewis²⁷), diuretin, theophylline, digitalis, ammonium chloride or nitrate and sodium mercurisalicylallylamido acetate. The number of the methods suggested is evidence enough of the lack of reliability of any one. In the case described, death occurred soon after the second injection of sodium mercurisalicylallylamido acetate. But Bernheim in 1,000 injections did not observe the slightest toxic symptoms from it. Herzky, Brunn, Agnew and Barker and O'Hare²⁸ have all had the same innocuous results. In view of this, the sodium mercurisalicylallylamido acetate can in no way be held

22. Holmes, W. H.: Lipoid Nephrosis, Illinois M. J. **54**:300, 1928.

23. Aldrich, C. A.: A Study of the Clinical Course of Generalized Edema, J. A. M. A. **84**:481 (Feb. 14) 1925.

24. Fanconi, G.: Zur Oedemfrage, Jahrb. f. Kinderh. **110**:12, 1925.

25. Von Koranyi, A.: Pathogenese der nephrotischen Wasser-Retention, Mitt. d. Gesselsch. f. inn. Med. u. Kinderh. in Wien. **24**:15, 1925.

26. Epstein, A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167, 1922.

27. Lewis, D. S., and Seriver, W.: The Response of Chronic Nephrosis to Parathyroid Medication, Ann. Int. Med. **2**:66, 1928.

28. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, J. A. M. A. **91**:2060 (Dec. 29) 1928.

responsible for the premature termination of this case. That it did any good is likewise unproved.

The fourth stage, the end-result of lipid nephrosis, is demonstrated in case 2. The material of this case was placed at my disposal by Dr. Milton Bohrod of the University of Illinois Research Hospital.

LIPOID NEPHROSIS WITH NEPHROTIC CONTRACTION

CASE 2.—History.—A white, Irish-American painter, 26 years old, first entered the Cook County Hospital on April 14, 1928. He said that he had had a chancre in 1927, for which he took eleven injections of neoarsphenamine and thirty of mercury. During the "rest period" following this first course, and just as he was about to start a second, he began to have attacks of abdominal colicky pains and diarrhea. These cleared up, but a generalized edema set in. The swelling was noticed first and most severely in the legs, but it did not there subside on rest. It slowly spread to the abdomen and face.

Physical Examination.—He was somewhat dyspneic on exertion, but there was no orthopnea. A mild cough was associated with a pharynx that showed injection. A slight pain in the chest followed for a short time. Dullness and distant breath sounds were obtained over the right lower pulmonary lobe. But this soon subsided. The abdomen was moderately distended with fluid. The heart was not enlarged.

Laboratory Examination.—He appeared pale, but examination of the blood showed that the hemoglobin was fully 80 per cent and the erythrocyte count 4,000,000. The blood pressure was normal, 126 systolic and 84 diastolic. The Wassermann reaction was negative. The blood chemistry showed a urea nitrogen of 20 and a creatinine content of 1.7 mg. per hundred cubic centimeters. There was marked albuminuria, also a few granular casts but no red blood cells in the urine. The Mosenthal test showed good power of concentration (1.030).

Clinical Diagnosis.—The clinical diagnosis rested between lipid nephrosis and parenchymatous nephritis (mercurial).

Further Course.—The patient was released from the hospital on May 2, 1928, apparently recovered, but he returned on June 11 with a recurrence of his first clinical picture. At this time, the blood cholesterol was found elevated to 416 mg. per hundred cubic centimeters. While the patient was in the medical ward, a swelling developed in the region of the thyroid gland. There was great pain, with local heat and induration with central fluctuation. Aspiration yielded thick pus. A suppurative thyroiditis was diagnosed. The abscess was opened and drained. It healed completely, and the patient left the hospital late in June.

In August, he suffered a second recurrence of the edema, and entered the University of Illinois Research Hospital. He was found to have a generalized anasarca, ascites and a bilateral pleural effusion. The heart was not enlarged. The blood pressure was normal, about 115 systolic and 70 diastolic.

Laboratory Examination on Third Admission.—Paracentesis yielded 5,500 cc. of a pseudochylous fluid, the specific gravity of which was 1.004. No doubly refracting lipoids were found in it. Its lipid was all isotropic.

The renal function was now distinctly impaired. On the Mosenthal test, the night urine equaled the day urine in quantity, and its specific gravity varied only from 1.007 to 1.010. Only 2 per cent of the phenolsulphonphthalein was excreted in three hours. There was severe albuminuria with few hyaline casts, but no red blood cells.

Blood chemistry returned successive cholesterol readings of 714, 1,136, 384, 455 and 625 mg. per hundred cubic centimeters. The nonprotein nitrogens were 45, 51, 46 and 65. The creatinines were 3.76 and later 4.29. The carbon dioxide-combining power of the plasma was 23. The chlorides returned 651 and 597 mg. per hundred cubic centimeters.

Anemia had developed with 43 per cent hemoglobin, an erythrocyte count of 2,260,000 and a leukocyte count of 7,000 per cubic milligram. The basal metabolic rate was depressed to minus 26 per cent. The Wassermann reaction was negative.

Clinical Diagnosis.—The clinical diagnosis still rested between lipoid nephrosis and chronic tubular nephritis of syphilis, mercurial or arsenical origin.

Further Course.—Sodium thiosulphate was given intravenously, because of the possibility of metallic poison. Clinically, the patient recovered.

He returned, however, on several occasions with a fourth, fifth and finally a fatal sixth recurrence in November, 1928, seven months after the onset of the illness. Even at the last attack, the blood pressure was only 118 systolic and 90 diastolic, and there was no cardiac hypertrophy or retinal changes. The patient suffered, however, from intermittent diarrhea, nocturia, polyuria and nausea and vomiting, which became progressively more severe until his death.

Postmortem Examination.—There was slight edema of both feet and ankles. The abdomen was greatly distended by 8,000 cc. of opalescent, yellowish, milky fluid. The peritoneum was dull, with nodular areas of thickening. The pericardial sac contained 75 cc. of clear, straw-colored fluid.

The heart was small and contracted. It weighed only 220 Gm. The myocardium was brown and friable.

The liver weighed 1,350 Gm. It was firm and yellowish brown. Its markings were indistinct. The spleen weighed 190 Gm.; its consistence was diminished.

The kidneys were both small. The right weighed 72 Gm.; the left, 92. The capsule stripped readily, leaving a smooth, yellowish-white surface with an occasional smooth elevation. The cortex was wide and deep yellow. The medulla was more brown and sharply demarcated from it.

Microscopic Examination.—There was at once evident, a striking disproportion between the pronounced interstitial and tubular changes and the slight glomerular and vascular changes in the kidneys. The latter were grossly insufficient to account for the former, but impressed one as being rather a result of them.

The tubules were widely separated by the marked increase of interstitial tissue. In the medulla, Henle's loops and the collecting tubules were all widely dilated by homogeneous casts. In the cortex, some of the convoluted tubules were dilated; others were altogether collapsed. There was a diffuse atrophy of the renal epithelium, especially that of the convoluted tubuli, which were lined by low cuboidal cells. There was no desquamation, no hyaline droplets, no mitoses, no enlarged cells or other evidence of either active regeneration or active degeneration. Only a few, fine fat droplets were scattered through the epithelial cells of the convoluted tubuli of the first order. As compared with those in the first case described, the tubular changes had apparently become far advanced, but had quieted down.

The increase of interstitial tissue even exceeded the tubular atrophy in severity. In places, there were large areas in which the tubules had entirely disappeared, and only groups of glomeruli with dense interstitial tissue remained. This tissue was composed of lymphocytes, fibroblasts and groups of large

branched or swollen round cells. The cells of most of the latter groups were stuffed by isotropic and anisotropic fat. This interstitial tissue proliferation encroached on the glomeruli in the form of dense, concentric, pericapsular thickenings.

As compared with the usual picture of chronic nephritis or of renal arteriosclerosis, the glomerular changes which accompanied these severe parenchymatous ones were unexpectedly slight. Most of the glomeruli had a normal or but



Fig. 3.—Kidney; intact glomerulus surrounded by far advanced atrophy of the tubules, pericapsular connective tissue thickening and marked increase in the interstitial tissue. Mallory aniline blue; $\times 275$.

slightly decreased blood content. Their capillaries were discrete, with lumen somewhat narrowed in places, but with no synechiae. The tufts were somewhat smaller than normal. This shrinking gave an apparent slight increase in cellularity, but there was no actual proliferation or infiltration of cells in the tufts. The Bowman's spaces were dilated, and many contained a pink homogeneous content. The parietal capsular epithelium showed a slight enlargement and proliferation under the thick pericapsular ring of connective tissue.

In some of the glomeruli, an occasional capillary loop was seen with small lumen. Other loops were obliterated by fusion of their walls and almost complete melting of structure into a hyaline mass. An occasional whole glomerulus was similarly almost or completely reduced to a hyaline mass showing a few nuclei and other remnants of capillary structure. The medium-sized arteries were unusually tortuous, apparently slightly thickened, but otherwise unchanged.

The alveoli of the thyroid gland were dilated, lined by flattened cells, and contained a large amount of colloid. There were a few fat containing reticulum cells in the stroma. A branch of the thyroid vein contained serum with sufficient lipid to stain it orange with sudan III.

There were no other important histologic observations in this case, except for a small amount of fat in the liver cells and a large amount in the suprarenal glands.

Anatomic Diagnosis.—The anatomic diagnosis was: lipoid nephrosis, fourth stage, with contraction; pseudochyolous ascites and hydropericardium; atrophy of the myocardium, and increased lipid content of the suprarenal cortex.

Comment.—The fourth stage of nephrosis is contraction. Rarely is it permitted to reach this stage, unhindered. The chronic metabolic disturbance leads to a profound visceral cachexia, as noted in our case in the premature brown atrophy of the heart at the age of 26. The atrophied and waterlogged tissues are susceptible to infection. Somewhere in the prolonged course of the ailment, the patient may be carried off by a pneumococcic peritonitis, an incidental infection, a superimposed glomerulonephritis or a myocardial failure. But, on rare occasions, as in this case, a pure nephrotic contraction is permitted to take place.

Because most of the rare cases described were in syphilitic patients, Munk termed the condition, "chronic syphilitic nephrosis with contraction." He scoffed at the suggestion of the mercury or arsenic being culpable. Indeed, he considered the only rational treatment in these cases to be active antisymphilitic therapy. The suspicion of syphilis was entertained in my case, but the patient did not enter the hospital until after a vigorous course of treatment, and his Wassermann reaction was then negative.

Histologically, the picture was strikingly different from other forms of contracted kidney. In nephritis, the inflammatory glomerular damage shuts off the function and the blood supply of the tubules. These disintegrate and are replaced by scar tissue, which contracts. In arteriosclerosis, the glomerular anemia produces the same result. In the severe tubular injury of the kidney damaged by corrosive sublimate, actual necrosis of the cells occurs and eventually scar replacement begins. In my case of lipoid nephrosis with contraction there were indeed glomerular and vascular changes. But they were neither inflammatory nor sclerotic in type and in no way comparable with the extreme contraction changes. There was no tubular necrosis, glomerular dam-

age or arteriosclerosis which could adequately account for it, yet the kidneys were severely contracted.

An explanation for this contraction one finds in the interstitial tissue itself. Several desmoplastic factors work hand in hand. In the early interstitial tissue changes, the histiocytes proliferate to take up the circulating lipoid and the lipoid from the slowly deteriorating epithelial tubular cells. They become swollen with singly refractile fats and with cholesterol. This swelling and proliferation of the histiocytes shuts off or narrows the lymph channels. The lymph stasis, in turn, induces further connective tissue proliferation, just as it does, for example, in filarial elephantiasis. Furthermore, the cholesterol is in itself desmoplastic. Injected into the peritoneal cavity, it induces the formation of a granulation tissue which soon becomes sclerotic; absorbed into the renal histiocytes, it does the same. Mechanically, also, the cholesterol droplets block the lymphatics and in this second way also contribute the extensive connective tissue proliferation.

As the tubules atrophy, they are seen to be widely separated by the increased and fat-laden interstitial tissue. The increase in connective tissue about the glomeruli produces pericapsular thickening, which should be separated from the intracapsular thickenings derived from organized crescents. This mechanically constricts the glomeruli as it shrinks, particularly involving the periglomerular capillary and the afferent arteriole. The glomerular blood supply is thereby reduced. Here and there, a glomerular capillary loop collapses, and part of the tuft loses all structural definition melting into a hyalinized strand. The glomerular epithelium is also damaged by the glomerulonephrosis, and may suffer secondarily from the tubular atrophy. These factors, together, proceed to partial or complete hyalinization of some of the glomeruli. This, in turn, then aggravates the tubular and interstitial changes.

The markedly increased interstitial connective tissue shrinks. As it shrinks, the kidneys contract. As they contract, the medium-sized blood vessels are rendered tortuous, and the tangential sections usually give a deceptive appearance of thickening. Thus without necrosis, inflammation or arteriolosclerosis does the nephrotic kidney contract.

The anatomic picture of nephrotic contraction is usually labeled "nephritis interstitialis chronica fibrosa multiplex," because in most cases the contraction changes are found in islands scattered between the less severely involved tissues. With few exceptions, the nephrotic contracted kidneys are described as granular. Only in an occasional case, such as mine, has such a kidney been described as almost perfectly smooth (a "glatte Schrumpfniere") with diffusely uniform atrophy and contraction. Why was this nephrotic contracted kidney smooth,

and others granular? How does it come about at times that in one kidney there can be granular patches of contraction, and smooth ones?

An answer to this question was offered shortly by an obvious case of primary contracted kidneys (malignant nephrosclerosis) in which one side of the kidney was found perfectly smooth and the other side perfectly granular. Death had occurred in uremia.

On microscopic examination of this kidney, one found that in the smooth-surfaced part, the main artery was so severely narrowed that the blood supply to the parenchyma was diffusely and severely impaired. The diffuse glomerular damage led to tubular atrophy and interstitial tissue proliferation. Shrinking of this caused contraction. The tubular atrophy was so severe that no regeneration took place, and the surface was smooth.

In the granular contracted part, the main artery was not so severely narrowed. The blood supply was somewhat less impaired. Enough blood passed through to the tubules so that some of them could regenerate, to compensate for those which had atrophied. These groups of regenerating tubuli lifted the contracted surface into fine granulations.

While it is therefore the shrinking of the proliferated interstitial tissue and to a small extent the parenchymatous atrophy which produces contraction, it is the regeneration of groups of less severely involved tubuli which produces granulation. In my case of "glatte Schrumpfnier," the tubular damage was so great that no power of regeneration was left to disturb by granule production, the smooth contraction of the interstitial tissue.

Even in the third stage of interstitial tissue changes, nephrosis begins to change from a simple metabolic disturbance to a real disease of the kidney. In the fourth stage of contraction, manifest renal insufficiency supervenes. True, comatose uremia does not appear, but the urea nitrogen and creatinine pile up in the blood, the carbon dioxide combining-power of the plasma sinks, the urine assumes a low fixed specific gravity and a severe uremia develops. That the blood pressure rises slightly, if at all, and that the heart does not hypertrophy are only results of the concomitant metabolic disturbance, which leads to a premature visceral cachexia and atrophy. Generalized arteriolar spasm or sclerosis are also lacking. But in many details the clinical picture may closely simulate that of chronic nephritis.

In particular, chronic nephritis with a marked nephrotic component may be clinically identical with true lipoid nephrosis. The same hypercholesterolemia, doubly refractile lipoiduria and reversed albumin-globulin ratio may be present. The blood pressure may be low in both and the cardiac hypertrophy slight. The gross anatomic appearance may be the same. Even histologically, the lipoid and interstitial changes may be identical; the differentiation can be made only by the

finding of the presence or the absence of inflammatory changes and by the marked disproportion between the glomerular and the tubulo-interstitial changes.

No wonder, then, that the careful clinician hesitates to make the differential diagnosis. Yet it is of some importance to do so, for the prognosis of nephrosis is considerably better than that of nephritis, and the treatment differs. The clinician complains therefore with justice that he cannot wait for the microscopic postmortem examination to make the diagnosis. As far as I have been able to find, there is only one clinical test that might be offered to help establish the diagnosis before death. This is the congo red test, which will be described in connection with case 3.

The nephrotic kidney is abnormally and specifically permeable to this dye. The nephrotic kidney, be its nephrotic component ever so marked, is not, it is claimed, permeable to it. Why this difference is not known. But different they are, for on applying this test, the urine of nephritis remains colorless, and the blood serum long stays pink; the urine of nephrosis, on the other hand, turns pink promptly, as the dye is rapidly discharged from the blood. Only this test might help to differentiate nephrosis from nephritis with a nephrotic "Einschlag." More work needs to be done with it.

The test has also proved of great value in detecting otherwise hidden amyloidoses. The difficulty of detecting amyloidosis before it is irreparably far advanced is well known. The ease with which even earlier stages may be obscured by other conditions, particularly by lipid nephrosis, is exemplified by case 4.

LIPOID NEPHROSIS WITH AMYLOIDOSIS

CASE 3.—History.—A colored woman, 30 years old, had since the age of 17, from time to time, acute exacerbations of a so-called "chronic rheumatism" in her right shoulder. When she was 25 years old, during such an attack, the right shoulder was incised and curetted. It reopened spontaneously twice after that and discharged thick pus. The last time was two years before the examination, and during this attack she suffered a generalized edema. She recovered shortly, however, and was discharged.

She was then apparently well until one month before her present entrance; at this time, she was operated on for some pelvic complaints. The fallopian tubes and ovaries were found buried in plastic adhesions, and were removed. The day after the operation, pain began in the left shoulder, and the face became swollen. The legs began to swell while the patient was still in bed, and then the abdomen. This attack was similar to that two years before, but instead of subsiding, it steadily became worse.

Physical Examination.—The patient finally reentered the hospital with severe edema of the entire body, and huge ascites which prevented accurate palpation of the liver and spleen. The heart was not enlarged. The blood pressure was 108 systolic and 76 diastolic.

The left shoulder was swollen, tender and painful, but not hot. Aspiration of it yielded thick, sterile pus. The muscles of the right shoulder were atrophic. Overlying them was the scar of the old arthrotomy.

Laboratory Examination.—The x-ray picture showed a destructive process in the head of both the left and the right humerus. The chest was clear. The leukocyte count was 6,500.

There was a severe albuminuria with many hyaline and granular casts, but no red blood cells. Doubly refractile lipoids were found in the urine. The total output was about 1,300 cc. per day with a specific gravity varying widely from 1.005 to 1.020. The Mosenthal test showed a good power of water concentration (specific gravity 1.022) and a low night urine (230 cc.).

Blood chemistry returned 10 mg. of urea nitrogen per hundred cubic centimeters and a cholesterol content of 400. The albumin content of the serum was severely reduced to the low level of 0.38 per cent, while the globulin maintained its normal average of 1.74 per cent.

Clinical Diagnosis.—The clinical diagnosis was: lipoid nephrosis or chronic nephritis and tuberculous arthritis of both shoulders.

Three days before her death, the patient suddenly felt a chill, followed by severe abdominal pain and the rising temperature of peritonitis. Paracentesis yielded 4,000 cc. of a green seropurulent fluid in which streptococci, but no pneumococci, were found.

Postmortem Examination.—There was a generalized anasarca. The abdominal cavity contained 1,000 cc. of yellowish-brown, cloudy fluid. The intestinal loops were agglutinated by loose, fibrinous adhesions. Their serosa showed injection in longitudinal, parallel bands.

The right pleural cavity contained 100 cc., the left 600 cc., of slightly cloudy fluid which compressed the left lower pulmonary lobe. There was a tuberculous primary nodule in the right lower pulmonary lobe. Otherwise, the lungs were clear.

A fluctuating swelling in the region of both shoulder joints was associated with an abnormal mobility of these joints. When the shoulder joints were opened, the joint surfaces were found separated by thick, green purulent material. The margins of the articular cartilage of both humeral heads were deeply eroded; their articulating surfaces were relatively intact.

The myocardium was grayish brown and friable. The heart weighed 235 Gm.

The liver was enlarged to 2,140 Gm.; its consistency was somewhat diminished. The cut surface was reddish brown, with light yellow patches and deep purple acinar markings. The spleen weighed 130 Gm. and was softened. Its pulp was deep grayish red, its trabeculae indistinct.

Both kidneys were markedly enlarged. The right weighed 323 Gm.; the left, 345. The capsule stripped easily, leaving a light yellowish-gray surface with numerous, pinpoint-sized brighter yellow areas. The consistency was slightly decreased. On cut surface, the cortex was 10 mm. wide and light yellow with pink to yellowish-white patches up to 1 mm. in diameter. The medulla was purplish gray.

Microscopic Examination.—Almost all the renal glomeruli were markedly enlarged, filling an entire high power field. The glomerular spaces were obliterated by the subendothelial deposit of a homogeneous azurophilic material. By specific stains (congo red or gentian violet) this material was shown to be amyloid.

There was no increased cellularity. On the contrary, many of the glomerular capillaries were narrowed, and in places obliterated by this deposit. However, many patent, blood-filled capillaries were still present in the enlarged glomeruli. Only a few glomeruli were somewhat smaller and almost completely obliterated by the amyloid. Occasional fine fat droplets were scattered through the cells of the tufts. A pericapsular thickening of connective tissue about each glomerulus was evident.

Two types of convoluted tubuli could be distinguished. One type had a relatively low epithelium with many fat droplets in the basal portion of the cells. The lumen of these tubules contained many casts and free round cells with pyknotic nuclei and cytoplasm stuffed by doubly refractile fat. These were the tubules of the first order, close to the glomeruli. The second type of tubules, farther away, belonging to the third order, was free from fat, but had large epithelial cells, filled with hyaline droplets.

The stroma was diffusely increased. It contained many groups of foamy cells, in which large amounts of doubly refracting fat were deposited. Besides these lipophages, it contained small accumulations of round cells. Amyloid was deposited beneath the finest capillaries of the stroma and in the walls of the arterioles and the smaller arteries.

In the liver, amyloid was found by specific stains in the walls of the arterioles and smaller arteries. Small lipid droplets filled the liver cells in the periphery of the acini, but were restricted to the enlarged Kupffer cells in the central portions.

Amyloid was found also in the smaller arteries of the spleen and suprarenal glands. Lipoid granules were also found in the reticulum cells of the stroma of the pancreas.

Anatomic Diagnosis.—The anatomic diagnosis was: lipid nephrosis with extensive amyloid infiltration of the kidneys; amyloidosis of the liver, spleen and suprarenal glands; chronic pyogenic arthritis of both shoulder joints; diffuse fibrinopurulent peritonitis (streptococcic); ascites and serofibrinous pleuritis; fatty changes of the liver, and anasarca.

Comment.—No suspicion of amyloidosis was entertained in this case until microscopic examination of the kidneys revealed it. It was appreciated that a chronic pyogenic arthritis would cause amyloidosis, but it might just as well produce a simple lipid nephrosis without amyloid. Hepatic enlargement could also be completely accounted for by fatty changes without amyloid. Clinically there was nothing lacking to make it a simple, classic, irrefutable lipid nephrosis. Every symptom, sign and laboratory observation of a pure lipid nephrosis was present. Even at autopsy, the gross appearance indicated only the lipid changes.

It was with some surprise, therefore, that on microscopic examination of the kidneys an extensive amyloidosis was unearthed. In addition there was also present every histologic requirement for a lipid nephrosis. Similar cases of lipid nephrosis completely obscuring clinically even an advanced amyloidosis have been reported by others (von Mogens²⁹).

29. Mogens, N. von: Ueber die klinische Diagnose der Amyloidose mittels Kongorotinjektionen, München. med. Wchnschr. **75**:1883, 1928.

Pure amyloidosis may occur alone. In early stages, it causes no renal symptoms of its own. It rests indifferently under the basement membranes. Only when far advanced, does it lead to kidney damage. Pure lipid nephrosis may occur alone, produce a typical clinical picture and even proceed to renal contraction without the slightest trace of amyloid.

Nephrosis and amyloidosis may occur together, but the two histologic pictures retain their independence. Since early amyloidosis yields no symptoms, the clinical picture of lipid nephrosis with early or moderate amyloidosis is the same as that without it. Thus Fahr reports that in sixteen of nineteen cases of amyloidosis with marked edema, there was an associated lipid nephrosis. Of eleven cases of symptomless amyloidosis, only three showed some lipid changes; the rest, none. Advanced amyloidosis may, however, change the oliguria of nephrosis to polyuria, and it contributes to the process of nephrotic contraction. Therefore are contracted kidneys more common in lipid nephrosis with amyloidosis than in lipid nephrosis without it.

How to distinguish the two processes has been a problem. Lipid nephrosis does not cause amyloidosis. Amyloidosis does not necessarily lead to lipid nephrosis. For either condition may become far advanced without the other. When they appear together, the two are separate and distinct consequences of a common injury. Any focus of suppuration sends into the blood stream products of purulent destruction which are foreign bodies to the system. The repeated discharge of foreign proteins into the circulation leads to the deposition of amyloid (Jaffé³⁰). The same focus of cellular destruction which causes this amyloidosis also sends into the circulation those toxic products which upset the lipid-protein metabolism and induce lipid nephrosis.

Yet the clinical differentiation is of great importance. It is essential to detect early amyloidosis even if obscured by lipid nephrosis; for its discovery gives a different aspect to the prognosis and treatment in the case. Lipid nephrosis is comparatively benign (Steinitz³¹). Most of the patients are alive long after the first symptoms appear. Amyloidosis gives to the case a much more grave prognosis. It bespeaks a hopeless devitalization of the patient by the toxins of prolonged suppuration. It contributes a serious element to renal damage.

Indeed, it was long considered that once amyloidosis developed, it was irreversible, and the patients died. This was only because our methods of detecting it were so crude that it could not be diagnosed

30. Jaffé, R. H.: Experimental Amyloidosis in Mice, *Arch. Path.* **2**:149 (Aug.) 1926.

31. Steinitz, H.: Zur Prognose der genuinen Nephrosen, *Deutsche med. Wchnschr.* **51**:1906, 1925.

until irreparably advanced. Bennhold³² found that by applying the congo red test he could detect amyloidosis in its early stages, long before it gave any clinical symptoms. If this was then taken as an indication for medical treatment and the focus of suppuration was promptly dealt with, the patients recovered, and the amyloidosis gradually disappeared. Amyloidosis, if detected early, is not irreversible.

The congo red test has been used extensively in Europe. In the course of its application, it was found not only to be a sensitive test for early amyloidosis even when complicated by nephrosis, but to give a specific reaction in nephrosis which differentiated this disease even from chronic nephritis with a marked nephrotic component. I therefore tried it out in a few typical cases, to help introduce this valuable test into use in this country.

METHODS FOR CONGO RED TEST

Preparation of the Congo Red Solution.—Triple distilled water is sterilized twice at 15 pounds' (6.8 Kg.) pressure. The congo red is weighed out sterily, and a 1 per cent solution made up. This is resterilized by heating for ten minutes to just below boiling. It is then filtered through a sterile funnel. To make sure it was harmless, 10 cc. of the 1 per cent solution was injected intravenously into a rabbit. There were no ill effects. Then doses of 1 cc., 2 cc. and finally 4 cc. were injected into normal persons. There were no ill results. The solution, so prepared and certified, if kept on ice, can be used for two days.

Application.—Bennhold's original technic is an accurate quantitative one. The injections are made before breakfast or some time after a meal, so that the serum shall not be too milky. Ten cubic centimeters of the 1 per cent solution is injected intravenously. At the end of four minutes, as soon as the dye has been evenly dispersed in the circulation, 5 cc. of blood is withdrawn by a second venipuncture. The patient's bladder is emptied, and he is given a glass of tea or water. At the end of sixty minutes, with care to avoid hemolysis, a second 5 cc. sample of blood is drawn, and another sample of urine is obtained.

Reading and Interpretation.—The serums are compared in an Autenrieth colorimeter. The serum of the four minute sample is pink and represents 100 per cent concentration of the dye. To make sure that the pink of the serum is not the result of hemolysis, it is necessary only to add one drop of concentrated hydrochloric acid to a portion of it. Normal serum gives a white precipitate. Pink serum gives a blue precipitate if its color is due to the dye, a brown one (hematin) if it is due to hemolyzed blood. During the course of an hour, the congo red is slowly excreted through the liver. Normally, at the end of sixty minutes, the serum is a slightly lighter pink; about 80 per cent of it is left. The samples of urine are both colorless.

In nephrosis, however, the kidneys are, for no known reason, abnormally permeable to the dye. By the end of one hour up to 60 per cent of it may be

32. Bennhold, H.: Ueber die Ausscheidung intravenös einverleibten Kongo-rotos bei den verschiedensten Erkrankungen, insbesondere bei Amyloidosis, Deutsches Arch. f. klin. Med. **142**:32, 1923.

lost, so that the second serum is much lighter in color than the first. The lost dye is found in the urine. While the first sample of urine is normally yellow, that voided at the end of an hour is pink. This pink urine of the congo red test indicates nephrosis. It does not appear in any other condition, not even in chronic nephritis with a nephrotic component.

In amyloidosis, the dye disappears from the blood stream with such great rapidity that from 60 to 100 per cent of it may be lost within the hour. The second serum becomes practically colorless. But the lost dye is not found in the urine. The urine remains colorless. The dye disappears because amyloid has a specific affinity for congo red. The amyloid, wherever it may be in the body, grasps the congo red from the circulating blood.

Simplified Method.—To obviate the necessity of a colorimeter, Paunz, Nemeth,³³ Strasser³⁴ and later von Mogens tried various modifications of this technic. They planned to give such a suitable quantity of the dye that with any appreciable amyloidosis or nephrosis there would be enough change of color in an hour to be directly read by the naked eye. The method is otherwise the same as Bennhold's, but the reading is much simplified. The dose von Mogens employed was 0.08 cc. of the 1 per cent solution per kilogram of body weight. This is the method I used.

TABLE 1.—*Results with Congo-Red Test*

Condition	Serum 1	Serum 2	Urine 1	Urine 2
1.* Normal	Deep pink	Deep pink	Yellow	Yellow
2. Pulmonary tuberculosis (no amyloidosis)	Deep pink	Deep pink	Yellow	Yellow
3. Pott's disease (slight amyloidosis).....	Deep pink	Slightly fainter pink	Yellow	Yellow
4.* Tuberculous arthritis (severe amyloidosis)	Deep pink	Colorless	Yellow	Yellow
5.* Chronic nephritis with nephrotic component	Deep pink	Deep pink	Yellow	Yellow
6.* True lipid nephrosis.....	Deep pink	Faint pink	Yellow	Deep pink

A second case of lipid nephrosis with amyloidosis has not offered itself yet for trial. Strasser³⁴ discussed the possibility and is also waiting for such a case. The investigators mentioned have all had excellent results with this test. Prepared under the directions given, it has never caused the slightest toxic symptoms. If several tests are done together, not much time is consumed. It is the only clinical test offered which may help to differentiate a true lipid nephrosis from chronic nephritis with a marked nephrotic component, and which can detect an early amyloidosis before it is irreparable.

SUMMARY AND CONCLUSIONS

Pure lipid nephrosis does exist. It is primarily not a kidney disease, but a disturbance in lipid-protein metabolism, a "lipoid-protein

33. Nemeth, L.: Ueber den klinischen Wert des Nachweises der Amyloidose durch die Kongorotprobe, *Klin. Wchnschr.* **5**:1040, 1926.

34. Strasser, Ulrich: Zur klinischen Diagnose amyloider Veraenderungen mittels Kongorot, *Wien. Arch. f. inn. Med.* **14**:97, 1927; Die Kongorotprobe auf Amyloid bei nephrotischem Symptomenkomplex, *Med. Klin.* **25**:468, 1929.

diabetes." The kidneys are involved only because of their rôle as active excretory organs for the products of the disturbed metabolism. Renal changes start with hyperactivity of the renal epithelium. These proceed slowly to exhaustion atrophy and degeneration of the tubule cells. The sessile histiocytes of the renal stroma proliferate and take up lipoids from the blood stream and from the degenerated tubular epithelium. The proliferated interstitial tissue shrinks, constricting the glomeruli and contracting the kidneys. This shrinking produces a smooth renal contraction, a "glatte Schrumpfiniere." But if the tubules are not too severely damaged, some of them regenerate. This active regeneration renders the surface of the smoothly contracted kidney granular.

Not every renal lipid infiltration is a lipid nephrosis. True lipid nephrosis is probably rare. Its histologic requirements are marked renal interstitial changes, as described, and lipid involvement of the reticulum tissue all over the body. It is separated pathologically from chronic nephritis with a nephrotic component ("Einschlag") by the absence of inflammatory or arteriosclerotic changes and by the marked disproportion between the slight glomerular and vascular changes and the profound tubular and interstitial ones. Clinically, so far, the differentiation may be impossible, except that the congo red test may prove by many more trials to be reliable.

Amyloidosis and lipid nephrosis are separate and distinct consequences of a common injurious agent. Amyloidosis when superimposed on lipid nephrosis contributes to the renal damage and renders the prognosis grave. But each process may appear alone. Early amyloidosis gives no clinical warning of its progress. It can be detected before it is irreversibly advanced only by the use of the congo red test described.

Book Reviews

LA HIPERTENSION ARTERIAL: HIPERTONIA ARTERIAL O HIPERPIESIS Y LOS ESTADOS HIPERTENSIVOS HIPERTONICOS O DE HIPERPIESIA. By DOCTOR MARIANO R. CASTEX. Prologo del doctor H. Vaquez. Pp. 590. Buenos Aires: Humberto Andreotta, 1929.

The preface of this book on arterial hypertension is written by Vaquez. The famous French clinician expresses admiration for the courage of the author in assembling the mass of data on hypertension. It must have taken enormous patience, effort and time to have collected what amounts to the world's literature on blood pressure. The citations are often lengthy and verbatim, adding considerable bulk to the volume but serving the purpose of quoting the authors so well as scarcely to require further reference to the original articles. Every section of this book begins with a complete review of the literature, even to the finest ramifications of the topic under discussion, and is then followed by the author's modestly expressed personal experience and critical considerations. As a result of this uniform procedure, there is a certain monotony.

The first part is devoted to the physiology of blood pressure. Of all the factors considered, the nervous system is given dominance as the regulator of normal, as well as of abnormal, arterial tension. The section on capillary and venous pressure is one of the rare weak spots, from the bibliographic aspect.

The general problem of hypertension, the older theories of pathogenesis and the clinical phases are considered in the second part. The compensatory or teleologic theory is decisively rejected. Hypertension is always pathologic, according to the author, and should be combated as early as possible. The vascular crises are well reviewed. The capillaries are said to play no rôle in the genesis of hypertension. The symptoms are determined by the hypertension per se, by the causal factors and the coordinated effects they produce and by the somatic and psychic make-up of the individual. As to treatment, the Hippocratic principle "confluxio una, conspiratio una, consentientia omnium" is wisely chosen as the slogan. The author commits himself frankly on the great host of medicaments and physiotherapeutic procedures and expresses no enthusiasm for such regimens as the calcium-atropine therapy of Kylin. This is one of the best chapters in the book, especially because of its emphasis on the consideration of the complete picture of the patient and his environment. The details of treatment are clearly related to the various indications. However, the recommendation to remove all foci of infection as an absolute routine indicates that this wave of destructive enthusiasm has already gripped the South American continent. Furthermore, the author's insistence on the etiologic and pathogenic diagnosis of hypertension before treatment is instituted must be accepted philosophically in view of the bleak situation in regard to such diagnosis.

As to pathogenesis, the author has a message to deliver and he dwells long and hard on it. Hypertension is largely of nervous origin, in turn either central or reflex. The hypothalamus is the center of the plot and this is influenced from above in psychogenic hypertension, or directly by toxic, inflammatory, degenerative or mechanical insults, or reflexly from the peripheral nervous system. Hence, all one has to do is to decide which one of these influences is acting on the hypothalamic vasomotor centers (the existence of which not all physiologists admit as yet) and thus make a topographic, pathogenic diagnosis. What could be simpler? Unfortunately, the author admits that many factors often cooperate to make such diagnosis difficult. He shows good judgment in throwing out salt, blood cholesterol, normal protein intake and tobacco as of any importance, but he retains alcohol on the usual flimsy evidence. Toxic hypertension is simply ascribed to focal infection — and there are many foci.

In the third part the various types of hypertension are developed from the clinical point of view, with the foregoing pathogenic scheme of Kahler as the background. Paroxysmal hypertension is well discussed. Everywhere causal therapy is advised; everywhere the stimulation of the diencephalic center is the cause of the hypertension. Much space is devoted to hypertension in cardiovascular disease, with emphasis on the work of the Hering school. The important problem of the renal causation of hypertension is exhaustively treated and finally the entire subject wound up with the opinion that diffuse renal disease and hypertension are autonomous but coordinated phenomena, having a common causal factor. The treatment is simple: operative, chemotherapeutic, foreign protein, serums, vaccines, etc. Early tonsillectomy is recommended, except in full-blown uremia. Malignant nephrosclerosis is considered in the same general fashion. Uremia is caused by a toxemia from focal infection and is characterized by a chaos in protein metabolism, which is due to a general tissue disturbance or to an effect on the metabolic centers in the diencephalon. The theory of the vegetative centers is developed in all its German massiveness of detail so that every possible clinical variation is explained on the involvement of different centers for partial functions. One begins to wish for a judicious regulator of all these regulatory centers in such close quarters.

The author is a great believer in enterogenous toxemia, and presents his side of the question without bothering about the opposition. If a vegetarian is reported to have developed hypertension, extra-intestinal factors must have been at work. Digestive toxemia may cause hypertension by the usual toxic, mechanical or reflex routes. The liver helps to detoxicate. In the functional types, vaccine and foreign protein therapy are effective.

The association of hypertension with diabetes, gout, obesity, hypercholesterolemia, pregnancy, diseases of the ductless glands, etc., is uniformly explained by the involvement of adjacent diencephalic vegetative centers. The permutations and combinations obviously are infinite and satisfying to the author.

The result achieved in this book is a creditable encyclopedic bibliography on blood pressure, but no great light is shed on the difficult field surveyed. There is an open challenge to all who read between the lines of the 590 pages — to debunk the diencephalon or to establish it scientifically as an absolute oligarchy, before more clinicians are led astray by their physiologic or clinical colleagues.

EDEMA AND ITS TREATMENT. By HERMAN ELWYN, M.D., Assistant Visiting Physician, Gouverneur Hospital New York. Price, \$2.50. New York: The Macmillan Company, 1929.

This monograph represents a rather violent reaction to the Starling-Epstein theory of edema and the whole concept of the rôle of mechanical forces in the fluid exchange between the blood and the tissues. Following the school of Kraus and Zondek, the author presents the evidence and the arguments in favor of a regulatory center for water balance situated in the hypothalamus. This center acts through nervous pathways and by means of the "hormone" of the intermediate and posterior lobes of the hypophysis on the "constellation of electrolytes" in the cells of the various organs, tissues and vascular structures involved in water balance. The whole purpose of this regulation is to keep the volume of the blood plasma constant. The chief stimulus to the center is an increase in, or a threat to increase, the water content of the blood. Oliguria, of acute nephritic or cardiac origin, is the most important stimulus. The regulatory center responds by sending out nervous impulses or the "hormone" to decrease the rate of movement of water from the tissues to the blood; hence the edema in cardiac failure and in acute glomerulonephritis. The edema in nephrotic renal disease, and in war-edema, is due to a decreased intensity of function on the part of the water center and other centers around the third ventricle. This depression is presumably secondary to the general state of undernutrition. Edema, in general, is compensatory to prevent an increase of the blood volume. Oliguria in nephrosis is compensatory to prevent loss of protein.

Diabetes insipidus represents increased function of the water center with resulting increase in the rate of movement of water throughout the entire system responsible for the maintenance of the water balance. The action of posterior pituitary extract as an antidiuretic is taken as evidence of the existence of a true hormone elaborated by the hypophysis in response to stimuli from the regulating hypothalamic center. A similar argument, of course, would make "hormones" out of digitalis, quinidine and many other drugs, because they tend to restore some abnormal function to the normal state.

The author does not explain why the regulating center is unable to affect the rate of movement of water from the blood into the tissues and thus prevent edema. He makes the rather fatal assumption of identity in action between such widely divergent systems as frog's skin, pig's intestinal wall and vascular capillary membranes toward the passage of fluids through them. The Donnan equilibrium between serum and edema fluid, whether in vivo or in vitro, is not considered. The lack of obvious disturbances in water balance in completely sympathectomized cats is also not mentioned. The weak experimental evidence for the existence of hypothalamic centers for partial metabolic functions is fortified by verbally lucid teleologic reasoning, the glittering haze of which adequately obscures the numerous pure assumptions. Constant repetition and well timed emphasis lend a convincing background to the thesis that edema is always a disturbance in central regulation and that it is always to be explained by decrease in the rate of movement of water from the tissues to the blood, the opposite movement apparently being beyond the control of the center. The mechanism of thirst is fitted into the scheme somehow.

The difficulty with the whole explanation of edema on the foregoing basis is that all general edemas are explained alike, when clinical and experimental facts point to wide differences in the pathogenesis of edema and in the nature of the edema fluid. Furthermore, as Volhard has stated in a review of this book (*Zentralbl. f. inn. Med.* 50:1042, 1929), the author fails to consider those states of edema in which no disproportion can be demonstrated between the rate of inflow and the rate of output of water. The lack of edema in prolonged anuria and in many cases of fatal renal insufficiency with oliguria is also not explained. Volhard maintains, as he always has, that oliguria is usually the result and not the cause of edema. Elwyn does not indicate why rigid restriction of salt and water intake is in itself entirely inadequate in the management of many cases of edema.

In the chapters on treatment the usual principles are laid down and the various diuretics discussed along orthodox lines. Parathyroid hormone is not mentioned.

The good features of this monograph are the excellent review of the available, chiefly German, literature on the "vegetative system" the detailed description of the clinical studies on war-edema, the discussion of the water depots in the body and their response to various experimental procedures and, above all, the unerring clarity of diction and simplicity of style so characteristic of all of the publications of Elwyn.

To the clinician searching for an answer to the complex problem of the pathogenesis of the various clinical types of edema this monograph will give little consolation, unless the credulity of the reader outweighs his critical acumen. To the physiologist who is sufficiently irritated by the one-sided point of view developed by the author, the book should function as an excellent cerebral stimulant and lead to a critical experimental attack on the vegetative centers. So far, the speculation has completely outdistanced the facts.

THE ESSENTIALS OF MEDICAL DIAGNOSIS. By SIR THOMAS HORDER, K.C.V.O., M.D., F.R.C.P. (LONDON), and A. E. GOW, M.D., F.R.C.P. (LONDON). Price, \$5.00. Pp. 682. New York: William Wood & Company, 1929.

The preface to this book gives an excellent discussion of the problems involved in the teaching of beginning clinical medicine and physical diagnosis. It is emphasized by the authors that differential diagnosis must be thought of very early in

the examination of the patient, and the entire book is developed along this idea. The book is divided according to systems, beginning with the nervous system, to which at least one fourth of the entire space is devoted, as might be expected in an English text. Then come the cardiovascular system, the respiratory system, the digestive system, the urinary system, the blood and blood-forming organs, the joints, the ductless glands, the skin and its appendages and a short chapter on pyrexia. Emphasis is placed on all practical clinical points, and little space is given to theoretical aspects. The arrangement of the book is good, in which the discussion proceeds from anatomy, through physiology, physical observations, the clinical diseases and differential diagnosis. Some of the simpler laboratory methods are included but are necessarily brief. The illustrations are much fewer than in American textbooks, and are almost entirely anatomic or x-ray pictures, but are all to the point. There is also a good index. For its size the book is excellent and will prove particularly valuable to those of a clinical turn of mind.

THREE MINUTE MEDICINE. A SERIES OF BRIEF ESSAYS ON POPULAR MEDICINE.

By LOUIS R. EFFLER, A.M., M.D., Director of Education, The Toledo Academy of Medicine, 1927-1928. Pp. 459. Boston: Richard G. Badger, 1929.

This volume of 200 short, pointed sketches on all possible medical topics accomplishes successfully what it was meant to be—a series of brief essays on popular medicine. As the author states in the preface, these essays were a reply to the open challenge of the *Saturday Evening Post*, that organized medicine should come down to "simple, racy English" and inform the public. The public which read these essays in the *Toledo Times* have been informed well on a great many items of historical interest in medicine and related sciences. It is refreshing to note the absence of specific diagnostic and therapeutic advice with which the daily medical columns are so full these days. To the busy practitioner and the medical student these essays furnish an easy and appetizing introduction into medical history. To the publicity committees of medical societies, the organization that made these essays possible could well serve as an excellent precedent. The book is well printed and free from errors except for a few amusing slips in the essay on Nobel Prize winners. Every physician's waiting room should have a copy.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG:

II. TAGUNG. HERAUSGEGEBEN VON PROF. DR. BRUNO KISCH, KÖLN. Price, 15 marks. Pp. 177. Dresden: Theodor Steinkopff, 1929.

The proceedings of the second meeting of the German Society for the Study of the Circulation seem to justify its establishment as a separate group with not only a specialized interest in a limited field, but broad contacts in many related fields because of the universal importance of the circulation in health and disease. For these reasons the various articles should prove of interest to the general internist, the cardiologist and the physiologist. Thus, there are papers on arteriosclerosis and old age, vascular damage by irradiated ergosterol, the cardiac output in hypertension, effects on blood pressure of obstruction of the external carotids in rabbits, rhythmic volume changes of vascular origin in the rabbit's ear, the physical registration of heart murmurs, the pathogenesis and treatment of edema, historical review of the use of digitalis as a diuretic, to mention only the most representative topics. This publication is a fitting addition to the well known *Zeitschrift für Kreislaufforschung*.

THE VALUE OF ACID NEUTRALIZATION IN THE TREATMENT OF GASTRIC AND DUODENAL ULCERS*

WALTER LINCOLN PALMER, M.D.

CHICAGO

The treatment for gastric and duodenal ulcer has long been one of the most disputed subjects in the field of medicine. This situation is due to the fact that no method is entirely satisfactory, and yet all of the various procedures seem to possess some merit. A critical evaluation of their effect is difficult because of the characteristic tendency of the disease toward spontaneous remissions. In the majority of cases, little or no therapy is required to bring about a quiescent period.

The difficulty is increased by the lack of any definite objective means of determining when an ulcer has healed, except that of gastroscopy, a procedure not generally available, applicable or safe. The disappearance of the roentgenologic niche is sometimes considered to signify healing, but surgical experience has shown that an active ulcer may be found at operation even after the roentgenologist is no longer able to demonstrate a niche. The only other objective evidence of healing obtainable, the disappearance of occult blood from the stool, undoubtedly signifies a tendency toward healing but not complete reparation, for many ulcers are active and painful when they are not bleeding.

Subjective evidence of healing, i. e., freedom from distress, is no more reliable than the objective, for Berg¹ and others showed that the symptoms of ulcer subside even before the niche disappears roentgenologically. There is, then, aside from gastroscopy, no method of determining when an ulcer has healed or of measuring the rate of healing.

Gutzeit² noted that the first stage in the healing process is a subsidence of the inflammatory reaction about the ulcer. This is associated

* Submitted for publication, Dec. 23, 1929.

* From the Departments of Physiology and Medicine of the University of Chicago and the Cook County Hospital.

* This work was supported in part by grants from the Seymour Coman Fellowship Fund, and from the Douglas Smith Foundation for Medical Research, both of the University of Chicago.

1. Berg, H. H.: Die direkten Ulcussymptome des Ulcus duodeni, *Ergebn. d. med. Strahlenforsch.* **2**:251, 1926.

2. Gutzeit, K.: Die Gastroskopie im Rahmen der klinischen Magendiagnostik, *Ergebn. d. inn. Med. u. Kinderh.* **35**:1, 1929.

with or even preceded by a desensitization of the pain-producing mechanism, as is indicated by the rapid disappearance of spontaneous pain and the early transition from a positive to a negative "acid test." The pain of ulcer is due to the action of an irritant on a sensitive apparatus. The usual effective irritant and apparently the *sine qua non* of ulcer distress is free hydrochloric acid in adequate concentrations acting over adequate periods of time.³ Failure of the irritant to produce distress under such conditions must be attributed to desensitization of the pain-producing mechanism. This change is indicated by the disappearance of spontaneous distress and by the transition from a positive to a negative "acid test." It apparently represents an early step toward healing and hence may be used as a rough index of the rate of healing.

PROCEDURE

The purpose of this paper is to present data bearing on the rôle of free gastric acidity in the rate of healing of gastric and duodenal ulcer. In the experiments to be described, two groups of patients were subjected to substantially identical types of treatment except for the fact that in one, the so-called "alkali group," an effort was made to neutralize the free acidity throughout the entire digestive period, whereas in the other, the so-called "beef-tea group," gastric secretion was purposely stimulated in order to maintain as high a free acidity as possible. Conclusions were drawn regarding the results in each group by observing the rate of desensitization of the pain-producing mechanism.

The "acid test" was performed in the manner previously described⁴ and is illustrated in the following protocols.

Patient 6007, a man, aged 37, entered the University of Chicago Clinics, Aug. 6, 1928, with a history of ulcer of three years' duration. Fluoroscopic examination revealed a definite deformity of the duodenal bulb with direct visualization of the crater of the ulcer.

The "acid-test" on Aug. 10, 1928, was as follows:

2:50 p. m.: Stomach aspirated; 40 cc. of liquid obtained. Free acidity, 31; total acidity, 46. No distress present. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

2:57 p. m.: Slight gnawing epigastric pain appears.

3:03 p. m.: Pain increasing, cramplike.

3:35 p. m.: Gnawing epigastric pain, identical in type and location with patient's typical distress, continues. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

4:12 p. m.: Typical distress continues. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

4:55 p. m.: Typical distress continues. Stomach emptied; 350 cc. of liquid. Free acidity, 93; total acidity, 99.

3. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcer, *Arch. Int. Med.* **38**:603 (Nov.) and 694 (Dec.) 1926; **39**:109 (Jan.) 1927.

4. Palmer, W. L.: The "Acid Test" in Gastric and Duodenal Ulcer, *J. A. M. A.* **88**:1778 (June 4) 1927.

5:12 p. m.: Slight gnawing pain still present.

Medical treatment was instituted August 13, with subsequent complete and almost immediate relief from distress. The examination by means of the x-rays was repeated September 1; at this time, a definite deformity of the duodenal bulb was seen, and the crater of the ulcer visualized again, although less definitely than at the previous examination. The "acid test," August 30, was as follows:

4:15 p. m.: Patient had no pain. Stomach aspirated.

4:20 p. m.: Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

5:06 p. m.: No pain. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

5:10 p. m.: Slight gnawing pain in region of navel.

5:21 p. m.: Distress ceases.

5:29 p. m.: Pain reappears.

5:36 p. m.: Distress ceases.

5:39 p. m.: Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

5:49 p. m.: Gnawing pain in region of navel reappears.

5:55 p. m.: Pain ceases.

6:10 p. m.: No pain. Four hundred cubic centimeters liquid aspirated from stomach.

The roentgenologic examination was repeated on October 12, revealing again a definite deformity of the duodenal bulb, but the crater of the ulcer was no longer demonstrable. The "acid test" on October 10 was as follows:

9:10 a. m.: No distress. Stomach emptied: 45 cc. of liquid. Free acidity, 60; total acidity, 63.

9:25 a. m.: Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

9:45 a. m.: No distress. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

10:15 a. m.: No distress. Two hundred cubic centimeters of 0.5 per cent hydrochloric acid injected into stomach.

10:45 a. m.: No distress at all. Stomach emptied; 360 cc. of liquid. Free acidity, 108; total acidity, 110.

This case illustrates the manner in which the pain produced by the "acid test" may gradually lessen in severity and require a longer latent period for its production until finally the latent period exceeds the duration of the test, no distress occurs within the hour and a half of the observation, and the test is negative. Occasionally, one sees cases in which the change from the positive to the negative "acid test" comes suddenly, but usually it is gradual. The transition in this case roughly paralleled the disappearance of the crater as seen roentgenologically. Usually in gastric ulcer the test becomes negative long before the niche disappears entirely, and this seems to be true of the crater of duodenal ulcer, although in this type of lesion its disappearance cannot be followed as readily as in the larger penetrating niche of gastric ulcer. It is this transition, then, from a positive to a negative "acid test" and from spontaneous pain to no spontaneous pain, which has been used in

these experiments to indicate the rate of desensitization of the pain-producing mechanism, and as a rough index of the rate of healing.

The original plan was to assign alternately to two groups all of the patients with ulcer entering the Cook County Hospital, the only exceptions to be those with acute perforation or massive hemorrhage. It was soon found, however, that it was not practicable to carry out the experiment in this fashion among unsegregated ward patients; for this reason, one series was finished before the other was started. These two groups, known as the "alkali" and "beef tea" groups, were kept ambulatory and were treated alike in every respect, except as will be described later.

A number of the patients became free from symptoms within a few days after admission to the hospital, even though they were allowed to remain ambulatory and were given the general ward diet. The major-

TABLE 1.—*Groups Studied*

Alkali Group:		
Total number of cases.....		31
Released within 7 days.....		3
Acute appendicitis within 21 days...		1
Cases studied		27
Gastric ulcer	3	
Multiple ulcers	1	
Duodenal ulcers	23	
Average duration of symptoms.....	..	61 years
Complicated by some obstruction, clinically.		8
Later operated on.....	.	4
Beef Tea Group:		
Total number of cases.....		32
Released within 10 days.....		2
Intereurrent tuberculous pneumonia....		1
Intereurrent carcinoma of the gallbladder		1
Mentally unreliable		1
Cases studied (all duodenal ulcer).....		27
Average duration of symptoms.....		5.7 years
Complicated by some obstruction, clinically		8
Later operated on.....		1

ity of these became acid-insensitive also and consequently could not be utilized for study. The series under observation included, then, all of the patients with ulcer admitted to the wards for men during the experimental periods who had positive roentgenograms and remained sensitive to the "acid test" until the diagnostic study was completed, with the exception, of course, of those whose ulcers were complicated by acute perforation or massive hemorrhage. Five of them became dissatisfied during the course of the experiments and insisted on leaving the hospital within a few days. These were excluded from consideration, as were four who developed complicating conditions or who were discovered to be mentally unreliable. Table 1 summarizes the data on the groups selected and shows which cases in each group were discarded.

The alkali group comprised twenty-three cases of duodenal ulcer, one of multiple gastric and duodenal ulcer and three of gastric ulcer, whereas the beef tea group was composed of twenty-seven cases of duodenal ulcer. A comparison of the two groups might be criticized

because of this accidental difference, but such a criticism does not seem to me to be valid, for in my experiments there is no noteworthy difference between the response of the 'pain-producing mechanism of gastric ulcer to the usual forms of therapy, and that of duodenal ulcer. The two groups of twenty-seven cases may be regarded, I feel, as strictly comparable; for the average duration of symptoms and the frequency of outlet obstruction were practically the same in each. The fact that more cases were finally submitted to surgical measures in one group than in the other is of no significance, for various other factors were determinative in this regard.

TABLE 2.—*Scheme of Management*

Time, A. M.	Alkali Group	Beef Tea Group
7:00.....	90 cc. milk and cream	90 cc. milk and cream
7:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
8:00.....	90 cc. milk and cream	90 cc. milk and cream
	240 cc. cream of wheat	240 cc. cream of wheat
8:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
9:00.....	90 cc. milk and cream	90 cc. milk and cream
9:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
10:00.....	90 cc. milk and cream	90 cc. milk and cream
	240 cc. of rice	240 cc. of rice
10:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
11:00.....	90 cc. milk and cream	90 cc. milk and cream
11:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
12:00.....	90 cc. milk and cream	90 cc. milk and cream
P. M.	240 cc. custard	240 cc. custard
12:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
1:00.....	90 cc. milk and cream	90 cc. milk and cream
1:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
2:00.....	90 cc. milk and cream	90 cc. milk and cream
	240 cc. cream of wheat	240 cc. cream of wheat
2:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
3:00.....	90 cc. milk and cream	90 cc. milk and cream
3:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
4:00.....	90 cc. milk and cream	90 cc. milk and cream
	240 cc. custard	240 cc. custard
4:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
5:00.....	90 cc. milk and cream	90 cc. milk and cream
5:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
6:00.....	90 cc. milk and cream	90 cc. milk and cream
6:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
7:00.....	90 cc. milk and cream	90 cc. milk and cream
7:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
8:00.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
8:30.....	Alkali in 90 cc. water	90 cc. 10% Liebig's beef extract
9:00.....	Entire gastric content removed, measured and titrated	
12:00.....	Stomach again emptied, contents measured and titrated	
Average daily dose of alkali: NaHCO_3 , 26.3 Gm.; CaCO_3 , 20.7 Gm.; MgO , 3.3 Gm.		
Average daily dose of beef extract: 135 Gm.		

The exact scheme of management used is shown in table 2. In both groups of patients, 90 cc. of milk and cream was given hourly from 7 a. m. to 7 p. m., together with five additional feedings of cereal or custard during the day. In the alkali group, alkaline powders were given in 90 cc. of water at hourly intervals from 7:30 a. m. to 7:30 p. m. and at 8 and 8:30 p. m. The powders consisted of calcium carbonate from 0.66 to 2 Gm. with sodium bicarbonate from 1.2 to 2 Gm., or heavy magnesium oxide 0.66 Gm. with sodium bicarbonate from 0.66 to 2 Gm. Occasionally, in cases in which an excessive night secretion existed, extra powders of calcium carbonate, 4 Gm., were administered between 9 p. m. and 12 midnight. If the evening aspiration revealed the presence of free hydrochloric acid, the hourly dose of alkali was increased, although in a few cases

even the largest powders failed to bring about a state of continuous anacidity. It was assumed that the 9 p. m. titration was an index of the peak of the daily acidity. The validity of this assumption may properly be questioned, but nevertheless it must be admitted that the average total daily dose of alkali, 26.3 Gm. of sodium bicarbonate, 20.7 Gm. of calcium carbonate and 3.3 Gm. of heavy magnesium oxide probably neutralized a large proportion of the free hydrochloric acid secreted during the digestive phase. The stomach was emptied of its entire content every night at 9 p. m. and again at 12 midnight.

In the beef tea group, hourly doses of 90 cc. of 10 per cent Liebig's beef extract, the secretagogue property of which has been shown by Pavlov⁵ and Ivy and McIlvain,⁶ were substituted for the alkali and water of the alkali group. This was done in order to stimulate gastric secretion and accentuate the difference in the free acid levels in the two groups. Milk and cream neutralize large quantities of hydrochloric acid, as was shown by Senator,⁷ later by Bönniger,⁸ and recently by Freezer, Gibson and Matthews.⁹ This effect was desirable in the alkali group, whereas in the beef tea series it had to be counteracted if the maximum contrasts were to be obtained in the free acid levels of the gastric content. It was thought that this could be accomplished best by the hourly feeding of beef tea.

Chart 1 shows a comparison of the effect on gastric secretion of water with that of 10 per cent Liebig's beef extract. The stomach was emptied per Rehfuß tube, then 100 cc. of water was injected; an hour later the stomach was again emptied, another 100 cc. of water injected, etc. The curve represents the free acid level. On another day, the experiment was repeated, 100 cc. of beef extract tea being used instead of water. The free acid curve is higher.

Chart 2 portrays a similar experiment carried out in one ten hour period. It is assumed in the later experiments that continued hourly administrations of beef extract resulted in continued stimulation of the secretory mechanism, but the possibility exists that this was not the case. It was not possible to know the exact level of gastric acidity minute by minute or hour by hour from day to day in any patient in either group, but there is reason to think that a definite difference in acidity between the groups existed. This hypothesis is supported by the fact that the average free acidity of the beef tea group at 9 p. m. was more than double that of the alkali group (table 5). The period of

5. Pavlov, J. P.: *The Work of the Digestive Glands*, London, Charles Griffin & Company, Ltd., 1902.

6. Ivy, A. C., and McIlvain, G. B.: *The Excitation of Gastric Secretion by Application of Substances to the Duodenal and Jejunal Mucosa*, *Am. J. Physiol.* **67**:124, 1923.

7. Senator, H.: *Ueber die diätetische Behandlung des Magengeschwürs*, *Deutsche med. Wchnschr.* **32**:95, 1906.

8. Bönniger, M.: *Zur Diagnosis des Ulcus ventriculi*, *Berl. klin. Wchnschr.* **45**:396, 1908.

9. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: *A Contribution to the Study of Alkalies as Therapeutic Agents*, *Guy's Hosp. Rep.* **78**:191, 1928.

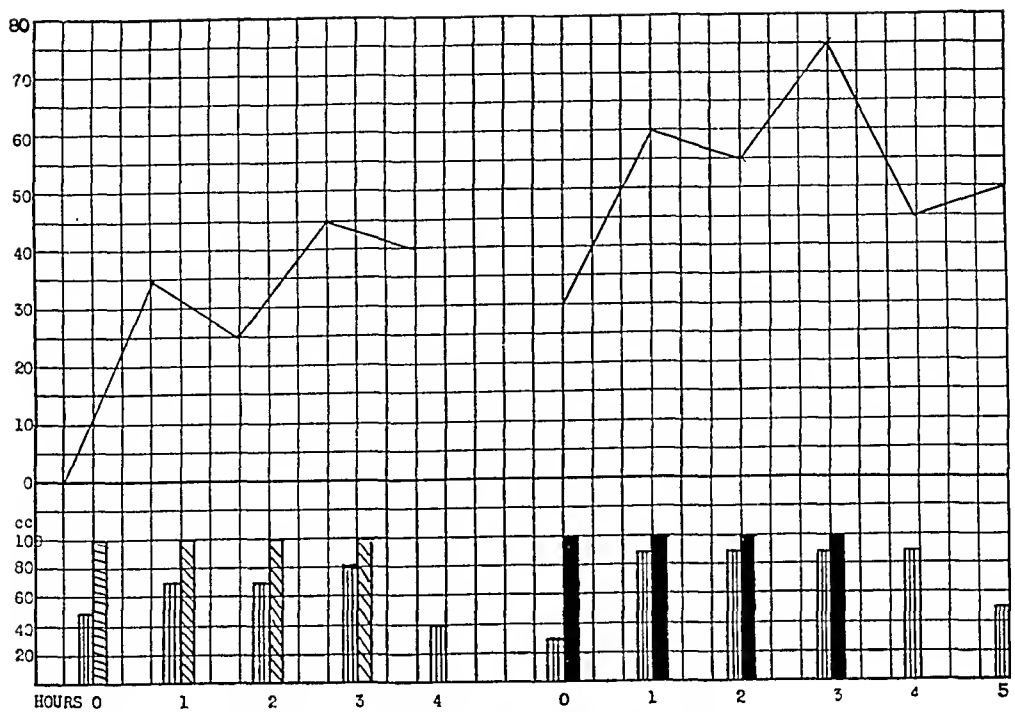


Chart 1.—A comparison of the effect of water with that of 10 per cent beef extract on gastric secretion. The curves represent the free acidity of the gastric contents. In the lower section of this chart and chart 2, the vertical lines indicate the amount of gastric contents removed; the diagonal lines, the amount of water injected, and the solid figure, the amount of beef extract tea injected. An interval of days occurred between the two determinations.

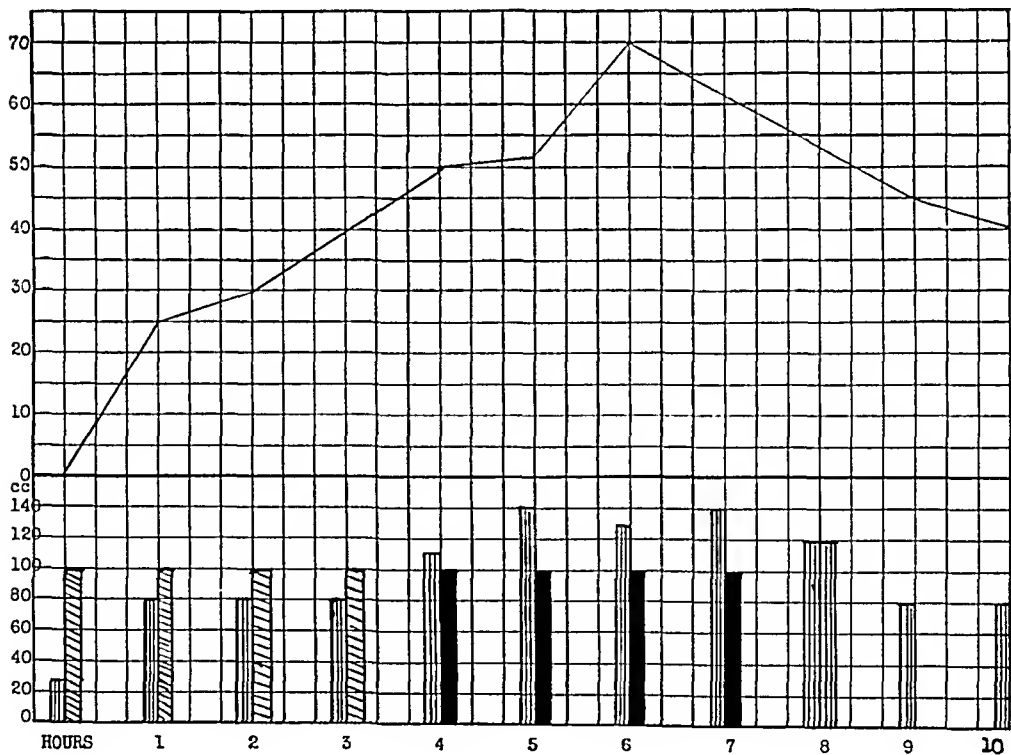


Chart 2.—A comparison of the effect of water with that of 10 per cent beef extract on gastric secretion. The curves represent the free acidity of the gastric contents over a ten hour period.

the administration of beef tea could not be continued indefinitely, and it was found best to vary it considerably, depending on the duration and degree of spontaneous distress. On termination of it, hourly water feeding was usually substituted for the beef tea feeding, followed several days later by the alkali regimen, as may be seen from a study of table 4.

RESULTS

Chart 3 portrays the difference in the rate of complete disappearance of spontaneous pain in the two groups, the average for the first being

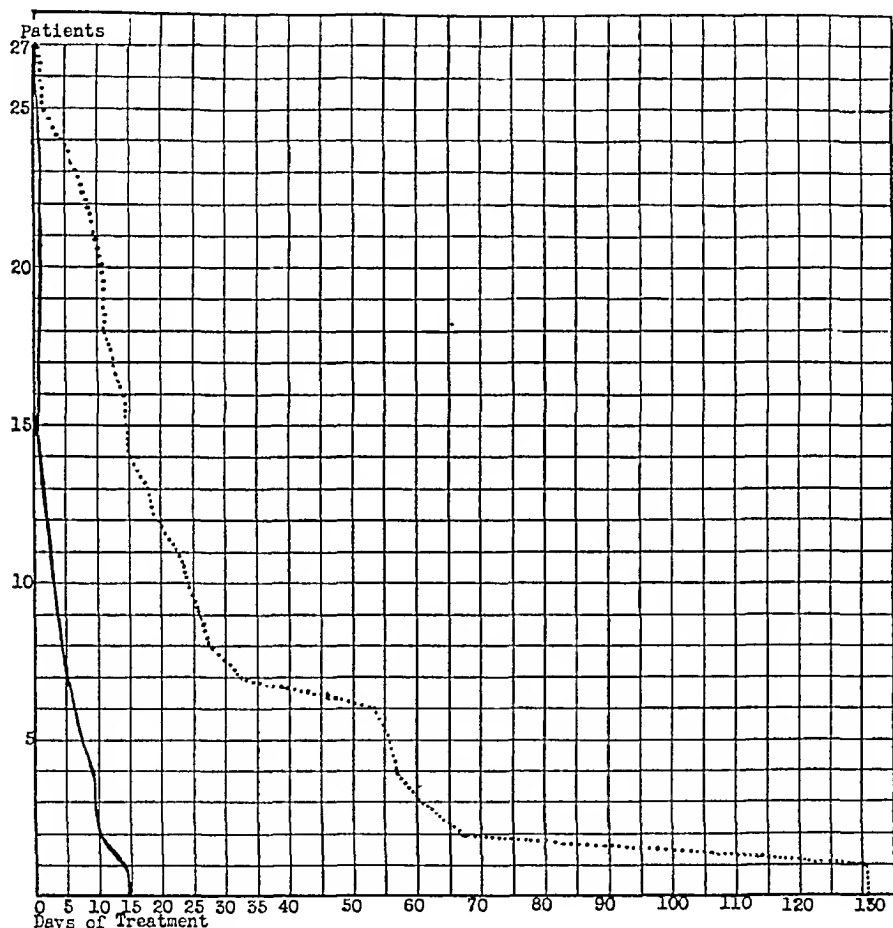


Chart 3.—Curves of the complete disappearance of spontaneous pain. The solid line represents the alkali group (average duration, 2.6 days); the dotted line represents the beef tea group (average duration, 26.6 days).

2.6 days as compared with 26.6 days for the second. It should be stated that most of the spontaneous distress in the alkali group occurred at night, owing apparently to uncontrolled night secretion. It is unusual to have distress from ulcer occur during that portion of the day in which half-hourly feeding of milk and cream and administration of alkali are continued.

TABLE 3.—“Acid Test” in Alkali Group

[illegible]

Table 3 presents a summary of the observations on the alkali group, showing not only the results of the "acid tests" but also the duration of ulcer symptoms prior to the patient's entering the hospital, the duration of spontaneous pain and the complications present.

Chart 4 portrays graphically the relationship between the duration of spontaneous pain and the positive "acid test" in the alkali group, the average duration of the former being 2.8 days, whereas that of the latter was 9.7 days. It should not be inferred that the "acid test" character-

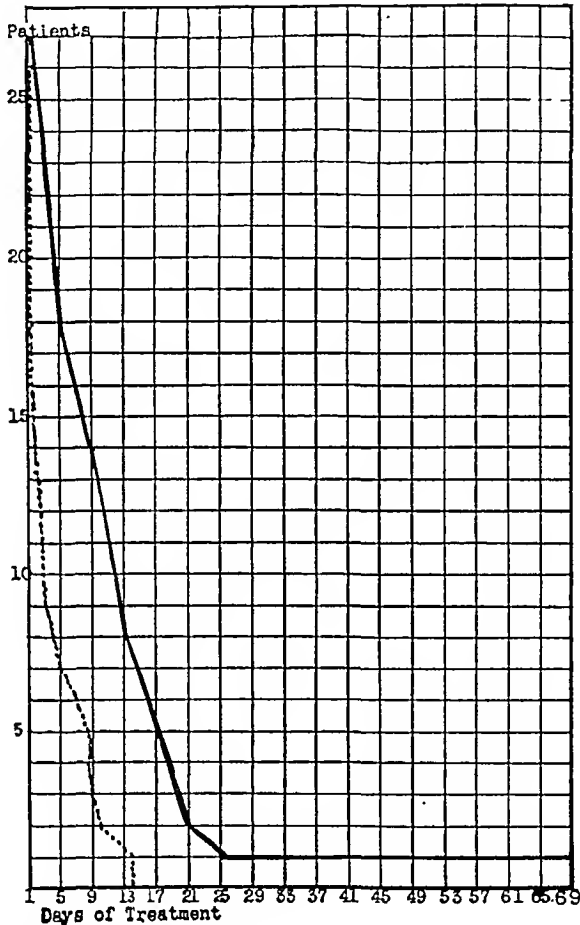


Chart 4.—Relationship of spontaneous pain and positive "acid test" in the alkali group. The dotted line represents persistence of spontaneous pain (average, 2.8 days); the solid line, persistence of positive "acid test" (average, 9.7 days).

istically remains positive for a week after spontaneous distress disappears. It does so usually in cases in which the type of alkali therapy described is employed, which is the "Sippy treatment" modified to conform to the conditions of the experiment, but not in those cases in which the distress disappears spontaneously. Under such conditions, the "acid test" usually becomes negative at about the time the spontaneous distress disappears, as will be noted later in comment on the

TABLE 4.—"Acid Test" in Beef Tea Group

Kind of Ulcer Shown by Roent- genogram	Duration of Spon- taneous Pain, Days	Days of Treatment																								Remarks																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
		1	5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93		97	101	105	109	114	118																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
1 Duodenal	3.0	0	*B+	W-	P-

* B = 90 cc. beef tea. + = positive "acid test." - = negative "acid test." W = 90 cc. water. P = alkali. A = absconded. R = returned. M = milk and cream only.

beef tea group and as may be seen by a careful study of the data presented. This difference is apparently due to the more prompt relief from distress induced by alkali therapy.

Table 4 summarizes the observations on the beef tea group. Case 15 is of especial interest here. The patient entered the hospital in such severe distress that it was necessary to keep him at absolute rest in bed. During the brief period of the administration of beef tea he continued to have severe pain and finally threatened to leave the hospital unless something was done to give relief. The beef tea was stopped,

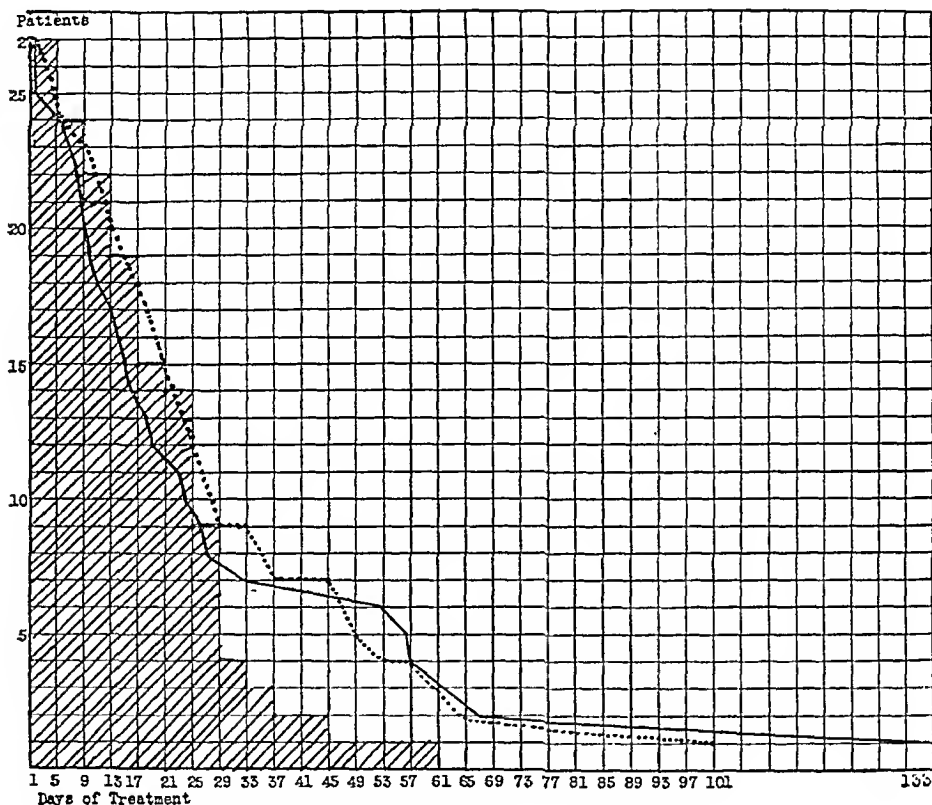


Chart 5.—Relationship of the administration of beef tea to the persistence of pain and the positive "acid test." The dotted line represents persistence of positive acid test (average, 26.9 days); the solid line, persistence of spontaneous distress (average, 26.6 days), and the diagonal lines, the period of administration of beef tea.

water substituted for it, and assurance given that the pain would diminish. It failed to do so, and after another short period the patient again threatened to leave the hospital. Alkalies were then given with the hourly doses of water, as in the regimen of the alkali group. The pain was at once relieved, although it did reappear at intervals during the following week. On the sixteenth day of experimentation and the eighth day of alkali therapy, it disappeared completely. In no other

case was the contrast between the two different forms of therapy so striking.

Chart 5 shows the relationship of the period of the administration of beef tea to the persistence of spontaneous pain and the positive "acid test." In this group, the average duration of spontaneous pain was 26.6 days and that of the positive "acid test" 26.9 days. This would seem to indicate that the cessation of spontaneous pain corresponded

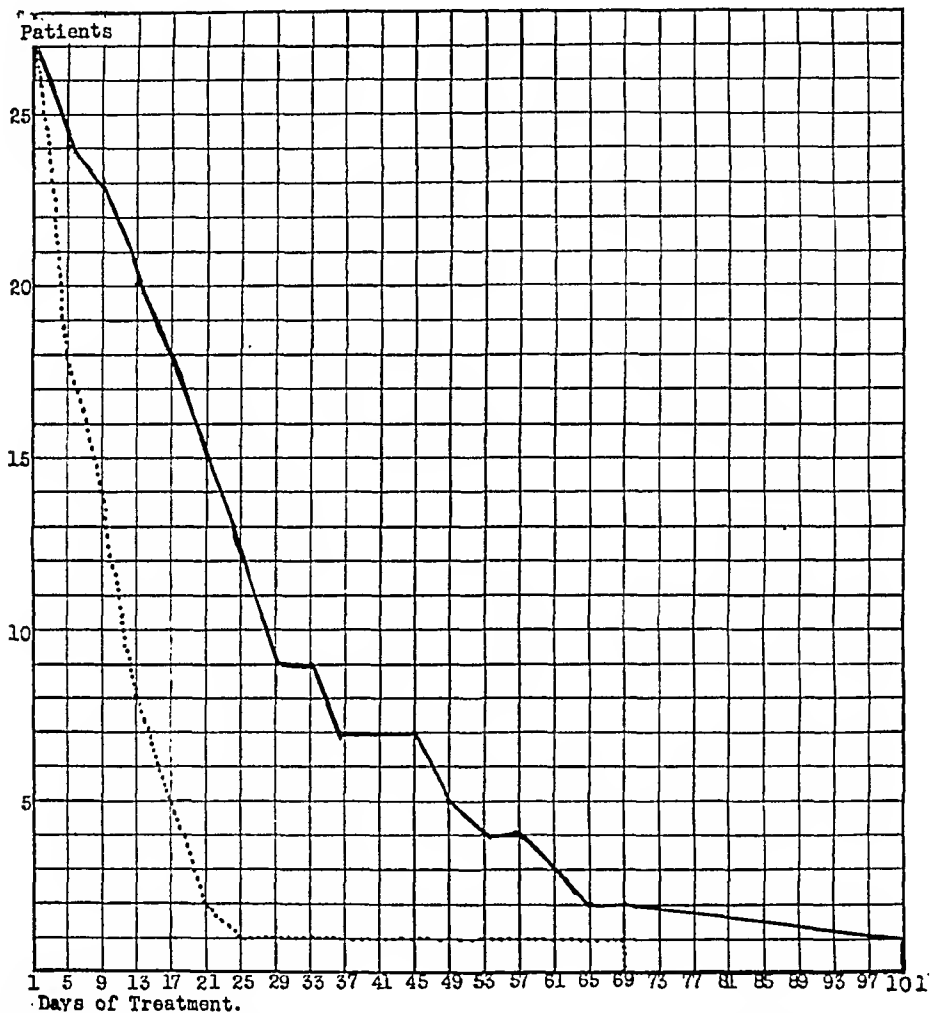


Chart 6.—Persistence of sensitivity to acid test. The dotted line represents the alkali group (average, 9.7 days); the solid line, the beef tea group (average, 26.9 days).

almost exactly with the transition from a positive to a negative "acid test." A study of the curves shows that this was not the case, and a more detailed study of the data presented in chart 6 will disclose further discrepancies. It is significant that in two thirds of this group the spontaneous distress disappeared during the period of administration of beef tea, and the "acid test" became negative before alkali therapy was instituted, while in the other third these changes did not occur until after the alkali therapy had been started.

Chart 6 gives a comparison of the rates of transition from a positive to a negative "acid test" in the two groups, the average length of time required for the alkali group being 9.7 days as compared with 26.9 days for the beef tea group.

A final summary of the experiments is given in table 5, which needs little additional comment. The method of selecting the cases has been described. The average duration of symptoms in one group is comparable with that in the other; the number of cases judged clinically to be complicated by more or less obstruction happened to be the same in each group; the numbers referred later for surgical intervention differed, but this fact has no bearing on the experiment, for the decision rested on entirely irrelevant considerations; the average duration of spontaneous and of induced distress was definitely less in the alkali group; the average quantity of free acidity of the gastric content

TABLE 5.—*Comparison of Alkali and Beef Tea Groups*

Points of Comparison	Alkali	Beef Tea
Number of gastric ulcers.....	4	0
Number of duodenal ulcers.....	23	27
Total	27	27
Average duration of ulcers in years.....	6.1	5.7
Number complicated by pyloric obstruction.....	8	8
Number later referred for operation.....	4	1
Average duration of spontaneous pain—days.....	2.8	26.6
Average duration of sensitivity to acid test—days.	9.7	26.9
9:00 p. m. aspiration—average quantity, cc.....	80.5	156.8
		Water 195.0
		Alkali 103.0
Average free acidity.....	13.0	23.8
		Water 30.7
		Alkali 17.0

obtained at 9 p. m. was much less in the first series than in the second. Apparently, the stomach emptied more rapidly under the alkali therapy than under the other regimens. It is difficult to know how much importance to attach to this fact, but when one considers that there was probably considerable gastric content present continuously in both groups from 7 a. m. to 7 p. m., an average difference of perhaps 80 cc. seems of questionable significance.

COMMENT

In many respects, the most significant result in these experiments is that two thirds of the patients in group 2 became free from spontaneous distress during the period of administration of beef tea and acid-insensitive without alkali therapy, indicating thereby desensitization of the pain-producing mechanism. This was to have been expected, of course, from the fact that the majority of ulcers become symptom-free and presumably acid-sensitive without any particular treatment. Any form of therapy usually suffices to bring about a period of remission.

This desensitization of the pain-producing mechanism, whether spontaneous or induced, apparently indicates that some progress has been made by the reparative processes in the ulcer. Stimulation of gastric secretion by means of the hourly feeding of beef tea did not stop them; it did not stop the natural tendency of the ulcer to heal spontaneously. This constitutes further evidence that, regardless of what the etiology of ulcer may be, and regardless of the cause of chronicity, the natural and usually the dominating tendency in any given ulcer is toward healing.

The next most significant observation is that neutralization of the gastric free acidity by means of alkalis definitely increased the rate of desensitization of the pain-producing mechanism. There is reason to think that some correlation exists between this and the healing process, that desensitization signifies some progress toward healing. The conclusion seems reasonable, therefore, that neutralization of the gastric free acidity favors healing. This may be due to protection of the ulcer surface from the destructive action of hydrochloric acid, to decreased gastric emptying time, as Dragstedt¹⁰ suggested in his experimental work, to diminished spasm or perhaps to other unknown factors. But regardless of what the explanation may be, healing apparently proceeded at a faster rate in the alkali group.

SUMMARY

1. Desensitization of the pain-producing mechanism occurred in both groups of patients.
2. The duration of the positive "acid test" exceeded the duration of spontaneous pain definitely in the alkali group, but only slightly in the beef tea group.
3. Stimulation of gastric secretion by the hourly administration of beef tea did not stop the healing process.
4. Attempted neutralization of the gastric free acidity definitely favored the healing process, as was indicated by the more rapid disappearance of spontaneous pain and the more rapid transition from a positive "acid test" to a negative "acid test."

10. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. 8:791 (May) 1924.

LABORATORY STUDIES IN EPILEPSY*

JOSEPH FELSEN, M.D.

NEW YORK

The data in these papers represent a continuation of the work published in 1924,¹ including a follow-up study over a period of from five to six years. Some of the patients originally studied were dropped because they had discontinued hospitalization, and others were substituted. Table 1 therefore serves to reconcile the old and new numbers, each number always indicating the same patient.

The general plan of study was to investigate by laboratory and clinical methods the various body systems (e. g., circulatory, digestive, ductless glandular, etc.), to draw tentative conclusions in regard to each system and finally to correlate the observations. A review of the literature was made after this work was completed. The cooperation of a specially trained nursing staff and the use of a locked ward and mimeographed forms for the accurate recording of observations were indispensable for the completion of these studies as they now stand.

Nearly all of the patients studied fell in the age group from 21 to 31 years, all being men. Wherever possible, normal controls of approximately the same age were secured from among patients who had no ascertainable disability or who were receiving physical therapy for healed wounds of the extremities.

THE BLOOD

THE FORMED BLOOD ELEMENTS, INTERPAROXYSMAL PERIOD

Interparoxysmal observations were made on the blood of fifty-seven epileptic persons. In each case, the blood was taken during a tranquil period, from twenty-four to seventy-two hours after the last seizure and not immediately preceding a subsequent one. Of course, one could not always be sure of petit mal attacks.

Platelet Count.—For the platelet count the method used was that of Wright and Kinnicutt. The average platelet count of healthy adults is from 300,000 to 350,000 per cubic millimeter. Five patients, all of whom showed a tendency to cutaneous petechial spotting during an attack, were studied. Two of these counts were distinctly low: 200,000 (no. 16): 103,760 (no. 65). No. 65 also had a prolonged coagulation time (nine minutes).

* Submitted for publication, Jan. 23, 1930.

1. Felsen, Joseph: Laboratory Studies in Epilepsy: I. Fractional Gastric Analysis, Arch. Int. Med. **34**:147 (Aug.) 1924.

Coagulation Time.—In the determination of the coagulation time, the gross test tube method of Lee and White was used. The accepted norm is from six to seven minutes. Of thirty-four patients, ten showed a lengthened coagulation time of eight minutes or more (nos. 2, 5, 19, 20, 21, 28, 49, 52, 61 and 65).

Bleeding Time.—Duke's method was used in the determination of the bleeding time, the upper limit of the norm being from two to three minutes. Of twenty-two patients examined, none exceeded this time, including the two having low platelet counts.

Fragility Test.—The fragility tests were made according to the method of Griffin and Sanford. Normally, hemolysis begins in a saline concentration of about 0.425 per cent and is complete in 0.35 per cent. Some authors place the lower limit at 0.32 per cent. Of the twenty-four estimations in this series, only one was worthy of note (from 0.405 to

TABLE 1.—Key to Numbering of Epileptic Patients Studied in Old and New Groups *

Old Number	Present Number	Old Number	Present Number	Old Number	Present Number	Old Number	Present Number
26.....	1	19.....	19	16.....	32	17.....	57
25.....	3	45.....	20	15.....	35	18.....	58
52.....	6	24.....	21	55.....	40	41.....	59
36.....	7	9.....	24	14.....	44	5.....	60
28-29.....	8	10-11-12.....	25	42.....	45	50.....	62
27.....	9	56.....	26	48.....	49	20-21.....	65
2.....	11	33.....	27	13.....	50	23.....	67
47.....	12	34.....	28	22.....	51	22.....	68
35.....	15	37.....	29	6.....	52	43.....	70
49.....	17	7.....	31				

* Thirty-eight patients of the original group remained for the subsequent studies; thirty-five other patients were substituted.

0.155). This fragility occurred in the patient (no. 65) having a low platelet count (103,760) and a prolonged coagulation time (nine minutes). There was a distinct tendency to petechial hemorrhages into the skin and conjunctivae.

Hemoglobin.—The hemoglobin content was measured by the Dare instrument checked against a prepared Sahli test. Of the forty-four patients examined, none showed any evidence of hemoglobinemia. Each had 85 per cent or above.

Erythrocyte Count.—The number of erythrocytes was estimated by means of the Levy counting chamber with Neubauer ruling, certified. Pipets were checked against the certified standard type. The dilution was 1 to 200. One hundred $\frac{1}{400}$ mm. areas were counted in duplicate. Of fifty-six estimations, nearly all averaged about 4,000,000 cells per cubic millimeter, indicating no marked cyanemia. None fell below 3,600,000.

Leukocyte Count.—Leukocytes were counted by the same method as the erythrocytes, except for a dilution of 1 to 20. Of fifty-six patients

examined, three (nos. 22, 46 and 54) showed a moderate leukocytosis not accounted for by any ascertainable existing infection. Eight showed a leukopenia of 6,000 or less (nos. 16, 19, 34, 37, 48, 53, 68 and 70).

Differential Blood Picture.—The differential blood picture was obtained by Wright's method. Of fifty-six patients studied, eleven (nos. 1, 6, 17, 20, 27, 28, 32, 39, 44, 49 and 50) showed a lymphocyte count of 31 per cent or over, one of them presenting a count as high as 52 per cent. In this latter case, the neutrophils amounted to 46 per cent. In all there were seven patients with neutrophilic counts of 60 per cent or less. The only other unusual observation was four instances of transitional cells amounting to 5 per cent or over.

Summary.—The interparoxysmal blood picture of fifty-seven epileptic patients may be summarized as follows:

1. Low platelet count: Two (of five selected patients) showed a low platelet count.
2. Prolonged coagulation time: Ten (of thirty-four patients) had a prolonged coagulation time. One of these also had a low platelet count.
3. Fragility test: One (of twenty-four patients) gave evidence of increased resistance of the blood to saline solution. This occurred in the patient having a prolonged coagulation time and a low platelet count.
4. Leukocytes: Three (of fifty-six) showed leukocytosis. Eight (of fifty-six) showed leukopenia.
5. Differential blood picture: Eleven (of fifty-six) showed moderate lymphocytosis. In four, there was an increase in transitional cells.

Review of the Literature.—Table 2 shows the essential results obtained by five other observers.

Patterson's² studies were apparently limited to distinct endocrine types. Some variations in the reported figures can probably be accounted for by the method used. Thus, Spangler³ used the Boggs instrument for obtaining the coagulation time.

There seems to be considerable difference in the reports on the total leukocyte count. This may be due to the time the specimen was taken, i. e., its proximity to an impending seizure or to a meal, or it may be due to some factor independent of the epilepsy (e. g., infection).

THE FORMED BLOOD ELEMENTS, PAROXYSMAL PERIOD

Observations were made on specimens of blood taken in each instance during a paroxysm or immediately on the cessation of the violent clonic movements. Complete examinations could be made in only a few cases.

2. Patterson, H. A.: Haematological Pictures in Endocrine Syndromes, *Am. J. Psychiat.* **2**:427, 1922-1923.

3. Spangler, R. H.: Blood Findings in Epilepsy, *Lancet* **1**:910, 1916.

Coagulation Time.—Normal coagulation time was shown by eight patients. Of these, two (nos. 61 and 65) had shown a lengthened coagulation time in the interparoxysmal period.

Fragility Test.—Normal fragility was found in seven cases and not essentially different from that observed during the interparoxysmal period.

Erythrocyte Count.—The erythrocyte counts on twelve patients were approximately the same as in the interparoxysmal period, except that of one patient (no. 65). In this instance, the lapse of ten months made comparison of the figures of the second seizure difficult.

TABLE 2.—*Comparison of the Observations on the Blood in Epilepsy (Interparoxysmal Period) Recorded in the Literature*

Author	Cases	Plate- let Count	Coag- ulation Time	Bleed- ing Time	Frag- ility Test	Hemo- globin, %	Red Blood Cells	White Blood Cells	Small Lympho- cytes	Eo- sino- phils
Onuf	19	106	4,895,000 to 5,405,000	7,802
Spangler	369	1.5 to 4.75 min. in 98 cases	84 in 100 cases	Normal	Normal	Normal	Normal
Craig Colony	10,800 to 34,200
Patterson	128	Leuko- cytosis
Smith	50-75	4,520,000
Felsen	57	Low in 2 of 5 selected cases	Pro- longed in 10 of 34 cases	Normal	In- creased resistance in 1 of 34 cases	Normal	Normal	3 of 56 leuko- cytosis; 8 of 56 leukopenia	11 of 56 increased	Normal

Leukocyte Count.—Of twelve patients, eight showed leukocytosis (nos. 9, 13, 31, 57, 61, 63, 64 and 65), two having counts of 17,800 (no. 13) and 18,400 (no. 65). It is interesting to note that the latter had shown a somewhat lower figure (12,200) during a seizure ten months previously.

Differential Blood Picture.—Eleven patients (nos. 4, 9, 13, 31, 56, 57, 58, 61, 63, 64 and 65) showed a lymphocytic preponderance of 31 per cent or over (three having counts of 50 per cent or above). All of them, except one (no. 61), had shown normal figures in the interparoxysmal period.

Summary.—Blood taken during paroxysm in a series of twelve epileptic patients showed essentially leukocytosis and lymphocytosis.

Review of the Literature.—Spangler³ stated that while the total leukocyte count during the interparoxysmal period is normal there is a leukocytosis at the time of and for twenty-four hours following a seizure.

He also stated that the coagulation time is shortened in the inter-paroxysmal period. Turner⁴ reported a similar observation during a seizure but a prolonged coagulation time following the fit. Others noted a marked prolongation of the coagulation time due to a diminution in the quantity of fibrin ferment just before a fit.

Féré⁵ noted a relative increase in the number of erythrocytes, due to the loss of fluid during an attack (secretions, sweat). Many of the cells diminish in size. There is also a destruction of hemoglobin and an increase in the number of platelets.

Pugh⁶ found a decrease in the number of leukocytes, beginning a few hours before a fit and often continuing up to the paroxysm. He also stated that during the fit the leukocyte count is high, and that it attains its maximum from fifty to seventy minutes after cessation of the fit. The

TABLE 3.—*Comparison of the Observations on the Blood in Epilepsy (Paroxysmal Period) Recorded in the Literature*

Author	Coagulation Time	Red Blood Cells	White Blood Cells	Lymphocytes	Remarks
Turner.....	Shortened	Increased	Coagulation time prolonged after fit
Féré.....	Increased	
Pugh.....	Increased	Increased	Decrease in white blood cells just before fit
Onuf.....	Increased	
Spangler....	Increased	
Wuth.....	Increased	Decreased	Eosinophilia after convulsion
Felsen.....	Normal	Normal	Increased	Increased	

increase is in the number of lymphocytes. There is also an increase in the number of eosinophils from two to ten hours after a seizure.

Onuf and Lograsso,⁷ studying two patients intensively at a definite time each day, found leukocytosis just before the fit and for many hours after its cessation. The extent of the rise is apparently inconstant and exists partly independent of seizures.

Wuth⁸ summarized the work on leukocytic reactions in relation to epileptic convulsions as set forth in table 4.

4. Turner, J.: Some Further Observations Bearing on the Supposed Thrombotic Origin of Epileptic Fits, *J. Ment. Sc.* **54**:638, 1908.

5. Féré, C.: Note sur l'altérabilité des globules rouges et sur la présence temporaire d'un grand nombre de globulins dans le sang des épileptiques après les accès, *Compt. rend. Soc. de biol.* **1**:213, 1889.

6. Pugh, R.: On Certain Blood Changes in Idiopathic Epilepsy, *Brain* **25**:501, 1902.

7. Onuf, B., and Lograsso, H.: Researches on the Blood of Epileptics, *Am. J. M. Sc.* **131**:269, 1906.

8. Wuth, C.: Blood Changes in Convulsions Especially in Epilepsy, *Bull. Johns Hopkins Hosp.* **38**:389, 1926.

Comment.—It appears difficult to reconcile these contradictory observations. It seems that a control observation of the blood picture during a period of freedom from disease is necessary for the accurate interpretation of a patient's blood picture in the epileptic state. Not infrequently a normal leukocyte but a high lymphocyte count is found for healthy adults. The frequent occurrence of a similar picture in children is well known. Moreover, in this series care was taken to rule out variations from the normal due to coexisting disease (e. g., diseases of the skin, asthma, influenza). A leukocytosis with a relative lymphocytosis occurs with unusual frequency during an epileptic paroxysm. This is probably not due to concentration of the blood, since the erythrocyte count remains approximately normal, the control being the blood picture of the same patient in the interparoxysmal period.

TABLE 4.—*Comparison of Observations on the Blood in Relation to the Seizure (Wuth)*

Before Seizure	During Seizure	After Seizure
Leukoeytosis (Riebes)	Leukoeytosis (Goediecke)	Leukoeytosis (Itten, Riebes, Schultz)
Leukopenia (Hartman, Di Gaspero)	Lymphopenia (Di Gaspero)	Lymphocytosis (Riebes)
Lymphocytosis (Schultz, Itten, Zimmermann, Gorrieri)	Lymphocytosis (Zimmermann, Schultz, Rhode)	Eosinophilia (Gorrieri, Di Gaspero, Schultz)
Eosinophilia (Gorrieri)	Eosinophilia (Zimmermann, Schultz)	

CHEMISTRY OF THE BLOOD, INTERPAROXYSMAL PERIOD

Examinations were made of the blood chemistry of fifty-five epileptic patients during the interparoxysmal period. All specimens were taken after an all night fast (usually fourteen hours). The Folin-Wu system of analysis was used for dextrose, urea, nonprotein nitrogen, uric acid and creatinine; Whitehorn's method for chlorides, and Levy, Rowntree and Marriott's method for p_H values. As regards the latter, Marrack and Thacker⁹ found that the error of the calorimetric method does not exceed 0.05 with normal plasma nor 0.12 with abnormal plasma. Variations occur due to temperature, venosity of the blood and hyperpnea. The Clark-Collip modification of the Kramer-Tisdall method was used for calcium and Hammerschlag's method for specific gravity.

Dextrose.—Of fifty patients, eight (nos. 9, 10, 13, 28, 44, 45, 49 and 63) had 75 mg. or less of dextrose per hundred cubic centimeters of blood, i. e., were distinctly hypoglycemic. One of them was markedly

9. Marrack, J., and Thacker, G.: The Reaction of the Blood in Epilepsy, Brit. J. Exper. Path. 7:265, 1926.

so (no. 63), and the value had no definite relation to a preceding or subsequent fit. Six patients were hyperglycemic (nos. 21, 24, 37, 40, 58 and 65), having 120 mg. or over per hundred cubic centimeters, and apparently this was not due to an existing diabetes or postprandial effect.

Urea Nitrogen and Nonprotein Nitrogen.—In fifty-five patients, urea nitrogen and nonprotein nitrogen were well within normal limits (from 14 to 20 mg. for the former and from 20 to 40 mg. for the latter).

Uric Acid.—The normal limits for uric acid are from 2 to 3 mg. Eight of forty-one patients had over 3 mg. (nos. 2, 5, 21, 24, 25, 34, 36 and 37), the uric acid in the blood of two (nos. 34 and 36) reaching as high as 4.01 and 5.23 mg., respectively.

Creatinine.—No essential deviations from the norm (from 1 to 2 mg.) were encountered (fifty-one patients).

Chlorides (as NaCl).—Of fifty-five patients, thirty-six (nos. 3, 4, 6, 8, 9, 10, 11, 12, 17, 20, 21, 24, 25, 26, 28, 29, 31, 32, 34, 37, 39, 40, 44, 45, 52, 55, 57, 58, 60, 61, 62, 63, 68, 69, 70 and 71) had 600 mg. or over. Figures of 800 (no. 69) and 850 (no. 62) were encountered, the former amount being found in the blood of a patient with epilepsy of moderate severity, the latter in that of a patient who at operation was relieved of a large intracranial endothelioma. Most of these figures can be accounted for by the salt-loving tendencies of these patients. This was proved by the necessity of placing those on a salt-poor diet under the most careful supervision, as they often spoiled three or four days' analyses by their surreptitious acquisition of salt.

Hydrogen Ion.—No abnormal concentrations of hydrogen ions were noted in nineteen examinations (p_H of from 7.6 to 7.8).

Calcium.—Sixteen patients showed no deviation from the norm (from 7 to 10 mg.) in respect to calcium.

Specific Gravity.—Twenty-four estimations of specific gravity ranged from 1.065 to 1.071 well within the normal limits (from 1.045 to 1.075).

Review of the Literature.—Table 5 summarizes the observations of various investigators in regard to the blood chemistry during a quiescent period. Dufour's¹⁰ case was that of a young woman who became epileptic after several injections of neoarsphenamine. The urea concentration of the quiescent blood was from 25 to 40 mg. per hundred cubic centimeters; the concentration rose a few hours before a seizure to 84, dropping to nearly the former figure by the next day.

Of variations in the chemical constituents of the blood of the epileptic patient examined during the quiescent period, the two most fre-

10. Dufour, H., and Semelaigne, G.: Sur un trouble humoral passager, précédant la crise d'épilepsie; variation de l'urée sanguine, Bull. Soc. méd. d. hôp. de Paris **44**:58, 1920; abstr., J. A. M. A. **74**:985 (April 13) 1920.

quently encountered by various investigators were those of dextrose and calcium. That these variations are not specific for essential epilepsy is apparent from the divergent opinions of many. I have been unable to verify the low calcium content and am convinced that all of the variations exist apart from any direct relationship to the pathologic condition known as "epilepsy." To be regarded as significant, they must occur with much greater constancy.

Reports on other constituents of the blood have been made. Thus, Hamilton¹¹ studied the bicarbonate, inorganic phosphorus and total

TABLE 5.—*Comparison of Observations on the Blood Chemistry in Epilepsy (Inter-ictal Period) Recorded in the Literature*

Author	Dex-trose	Urea N	Non-protein	Uric Acid	Creatinine	Chloride	pH	Calcium	Specific Gravity	Cases
Daly.....	Normal	1
Dufour.....	25 to 40 mg.	1
Boutter.....	11
Lennox.....	Normal	Normal	Normal	Normal	129*
Sherrill.....	Normal	High	Normal	6
Hamilton...	Normal	Normal	17
Marrack.....	7.3 to 7.5	—
Cullen, Bigwood, Myers	Low 7.3 to 7.43	—
Prior.....	Diminished	35
Bigwood....	Diminished	35
Pezzali.....	Normal	Normal	Normal	5
Felsen.....	Of 50, 8 hypoglycemia; 6 hyperglycemia	Normal (55 patients)	Normal (55 patients)	Of 41, 8 high	Normal (51 patients)	Of 55, 36 high	Normal (19 patients)	Normal (16 patients)	Normal (24 patients)	As stated

* Amino-acid normal.

fixed base in the blood of seventeen epileptic patients and found the amounts to be normal (HCO_3 , from 55 to 70 per cent by volume; P, from 2.6 to 6 mg.; total base, from 153 to 161 cc. 0.1 N). Spangler,³ examining twenty-one epileptic patients and three controls, found a lowered alkalinity of the blood (186 mg. as compared with the norm of 266 mg. of sodium hydroxide to a hundred cubic centimeters of blood). A similar result was obtained by Pugh,¹² and Dautrebande¹³ described an

11. Hamilton, B.: A Comparison of the Concentration of Inorganic Substances in Serum and Spinal Fluid, *J. Biol. Chem.* **65**:101, 1925.

12. Pugh, R.: The Alkalinity of the Blood in Mental Diseases, *J. Ment. Sc.* **49**:71, 1903.

13. Dautrebande, L.: Acid-Base Balance of the Blood in Epilepsy, *Compt. rend. Soc. de biol.* **94**:133, 1926; abstr., *J. A. M. A.* **86**:1323 (April 24) 1926.

alkaline substance which has no affinity for carbon dioxide in vivo, as was previously reported by Bisgaard, Tarlow and Norvig. Bigwood¹⁴ regarded epilepsy as a disturbance of the body's neutralizing mechanism (an alkalosis). This involves especially a concentration of blood plasma in calcium ions—an essential factor in the regulation of cellular excitability in general. In a study of thirty-five epileptic patients, he¹⁵ found that attacks occurred only if the alkalosis was accompanied by a low blood calcium. Claude¹⁶ and his co-workers, on the other hand, reported that induced alkalosis in dogs with epileptigenous lesions does not provoke epileptic seizures unless a toxic factor is present in addition.

Popea and Vicol¹⁷ found a diminution in the cholesterol content of the blood of sixteen epileptic patients suffering from frequent seizures.

Luck and his co-workers¹⁸ found the ammonia content raised in the blood of three of four epileptic patients after a seizure (the norm being 0.10 mg. per hundred cubic centimeters). They did not regard this of etiologic importance as an increased blood ammonia also occurs during starvation—a method often used to lessen the frequency of convulsions. They explained the uniformly high ammonia figures of Bisgaard and Norvig¹⁹ as being due to the method used.

Comment.—In the present series there appear to be no significant changes in the blood dextrose, urea nitrogen, nonprotein nitrogen, uric acid, creatinine, sodium chloride, hydrogen ion concentration, calcium or specific gravity. Almost all of the deviations from the norm checked at a subsequent examination one week later, after seven days of salt-poor diet, had returned to the average level. After comparison of these figures with those in the average run of cases in the same hospital, it seems that similar variations are encountered in nonepileptic groups, including patients without any ascertainable disability.

14. Bigwood, E. J.: L'équilibre physico-chimique du sang dans l'épilepsie, *J. de physiol. et de path. gén.* **22**:70 and 94, 1924.

15. Bigwood, E. J.: Blood Calcium Deficiency in Epilepsy, *Compt. rend. Soc. de biol.* **90**:98, 1924; abstr., *J. A. M. A.* **82**:926 (March 15) 1924.

16. Claude, H.; Raffin, R., and Montassut, M.: Rôle of Alkalosis in Epileptic Seizures, *Compt. rend. Soc. de biol.* **94**:1334, 1926; abstr., *J. A. M. A.* **87**:1160 (Oct. 2) 1926.

17. Popea and Vicol: Cholesterolemia in Epileptic Seizures, *Compt. rend. Soc. de biol.* **93**:749, 1925; abstr., *J. A. M. A.* **85**:1518 (Nov. 7) 1925.

18. Luck, M. J.; Thacker, G., and Marrack, J.: Ammonia in the Blood of Epileptics, *Brit. J. Exper. Path.* **6**:276, 1925.

19. Bisgaard, A., and Norvig, J.: Causation and Treatment of Epilepsy, *Hospitaltid.* **63**:49, 1920. Norvig, J.: Metabolic Anomalies in Psychoses, *Acta med. Scandinav.* **60**:211, 1924.

CHEMISTRY OF THE BLOOD, PAROXYSMAL PERIOD

The figures in table 6 represent the results of examinations of blood specimens taken from eleven patients, in each case immediately after the cessation of a paroxysm. The proximity of the epileptic ward nearly always enabled a technician to reach the patient before the seizure was over. Only single seizures are included. This was done in order to obtain some degree of uniformity, as the results obtained after single and those obtained after multiple seizures are not comparable.

Dextrose.—Three patients had a hypoglycemia below 60 mg. (nos. 13, 24 and 67). On one previous examination (interparoxysmal), patients 13 and 67 had low figures. Patient 24 was alternately high and low at two previous tests during a quiescent period. Of the remaining eight patients, nearly all showed a lower concentration of dextrose than on two other occasions.

TABLE 6.—*Chemistry of the Blood During the Paroxysmal Period (Eleven Epileptic Patients)*

Patient	Dex- trose*	Urea Nitrogen	Non- protein Nitrogen	Uric Acid	Creat- inine	Sodium Chloride	Hydro- gen Ion	Cal- cium	Specific Gravity
4.....	90.0	14.3	38.0	663.0	7.8
9.....	100.0	14.2	21.9	1.15	1.01	676.5
13.....	58.9	12.8	31.0	0.91
24.....	52.9	17.6	24.2
25.....	118.0	15.0	28.0	2.50	0.86	490.0
37.....	106.3	15.2	30.0	1.36	610.0
57.....	117.6	12.2	12.8	1.87	673.0	7.6	8.4	1.004
61.....	90.0	19.0	31.5	1.50	693.0
65.....	108.0	11.5	36.0	656.0	7.5	...	1.070
67.....	56.9	15.2	31.5	1.47	620.0
72.....	90.0	12.0	22.0	2.00	0.70	580.0

* Values throughout the table in milligrams per hundred cubic centimeters.

Other Observations.—The other chemical constituents were within normal limits. The work on the blood chemistry is rather fragmentary, because the patient would often leave the hospital before all of his examinations were complete and therefore no controls were to be had, i. e., during the quiescent period. These patients are not included in the studies.

Review of the Literature.—Table 7 summarizes the observations of other investigators on the chemistry of the blood immediately after a seizure. Chemical constituents other than those studied in my series have been studied in relation to seizures. Thus, Wuth⁸ reported an increase in the serum protein. In one case, Hamilton¹¹ found normal values for bicarbonate, phosphorus, total base, calcium and sodium chloride. Pugh¹² reported a diminution in the alkalinity of the blood both before and after a fit. Pezzali,²⁰ studying five epileptic patients,

20. Pezzali, G.: The Blood in Epilepsy, *Riforma med.* **39**:433, 1923; abstr., *J. A. M. A.* **81**:341 (July 28) 1923.

noted a decrease in cholesterol and an increase in calcium during seizure. Hypcholesterolemia was also reported by Popea and Vicol¹⁷ to have occurred in sixteen epileptic patients. Luck and his co-workers¹⁸ found an increase in the blood ammonia in three of four patients.

Comment.—Chemical examination of the blood of eleven epileptic patients immediately after seizure showed no changes other than those which might reasonably be ascribed to physical exertion.

EFFECT OF SALT-POOR DIET ON CHEMISTRY OF THE BLOOD

It was noticed in the course of some studies on the daily habits of epileptic persons that many of those with a most severe type of the disease had a voracious appetite for salt. This tendency did not appear to be present in a similar control group of nonepileptic persons. As an

TABLE 7.—*Comparison of Observations on the Blood Chemistry in Epilepsy (Paroxysmal Period) Recorded in the Literature*

Author	Dextrose	Urea Nitrogen	Nonprotein Nitrogen	Uric Acid	Creatinine	Chlorides	Hydrogen Ion	Cases
Daly.....	Normal with tendency to low values	4
Boutter.....	Normal	11
Lennox.....	Normal	Normal	Normal	Normal	1
Krainsky, Rhode, Allers	Increased
Wuth.....	Increased (1 case)	Increased (1 case)	Increased (1 case)	5
Pezzali.....	Normal	Normal	5
Felsen.....	Tendency to low values	Normal	Normal	Normal	Normal	Normal	Normal	11

illustration of this point, it was found that many patients exceeded the average daily requirement of 3 or 4 Gm. by from 40 to 60 Gm. With a view to noting the effects of an almost complete withdrawal of sodium chloride from the diet, a separate table and feeding hour were established for small groups. The distress caused by this measure necessitated the closest scrutiny and the use of a locked ward in most cases could not be prolonged beyond one week. The salt-poor diet of Friedenbergs was used.

Dextrose.—Six patients showed some increase in dextrose, i. e., over 120 mg. per hundred cubic centimeters (nos. 8, 21, 22, 62, 65 and 68). Of these, two (nos. 21 and 65) had previously shown mild hyperglycemia. Hypoglycemia, i. e., below 80 mg., was observed in four patients (nos. 29, 44, 57 and 60). Of these, one (no. 44) had previously shown a low figure.

Urea Nitrogen.—No unusual values of urea nitrogen were noted.

Nonprotein Nitrogen.—No unusual values of nonprotein nitrogen were noted.

Uric Acid.—Ten patients (nos. 11, 21, 34, 36, 39, 51, 62, 68, 69 and 71) had a blood uric acid content of over 3 mg. Of these, two (nos. 68 and 69) showed 6.25 and 7.3 mg., respectively; three (nos. 21, 34 and 36) had previously shown high figures. Several patients had unusually low blood uric acid, probably accompanying the increased elimination of fluid through the kidneys which regularly follows the use of a salt-poor diet.

Creatinine.—No changes in the creatinine values were worthy of note.

Chlorides (as NaCl).—After six days of almost total deprivation of sodium chloride, seventeen (nos. 3, 4, 5, 8, 10, 21, 34, 39, 40, 44, 48, 55, 57, 58, 61, 70 and 71) of forty-one patients still had a blood chloride content of over 600 mg.—41 per cent, as compared with 65 per cent with high figures before the salt-poor diet was instituted. Of the seventeen, all but two (nos. 5 and 48) had previously had high figures. On the whole, the general tendency was toward a definite, marked reduction in the chloride level, this level in two patients (nos. 29 and 51) reaching 330 and 350 mg., respectively.

Calcium.—No changes were found in the calcium content.

Specific Gravity.—The specific gravity showed no changes.

Review of the Literature.—Sherrill²¹ subjected four epileptic patients to a salt-free diet for ten weeks. The plasma chloride was considerably reduced, the most marked reductions occurring in the patients with higher figures at the outset, who also showed greater elimination in the urine. The urea, originally high, was reduced somewhat, and the blood sugar was unaffected. No therapeutic benefit was obtained.

Comment.—There appears to be no evidence that a salt-poor diet used for a period of six days has any effect on the blood chemistry other than reduction of the chloride content. This may be of importance, however, in connection with epileptic seizures associated with renal disturbance, and will be discussed later.

THE WASSERMANN REACTION OF THE BLOOD

The Wassermann test was performed on the blood of seventy-three epileptic patients. The technic employed involved the use of plain and cholesterolized antigens and the human hemolytic system. Inactivation was for fifteen minutes at 56 C., and incubation was at 37.6 C. Multiple positive and negative serums and antigenic, hemolytic and corpuscle

21. Sherrill, J. W.: Metabolic Observations in Psychiatric Cases, *J. Metab. Research* 5:129, 1924.

controls were used each day. Readings were made at once and after overnight retention in the icebox.

Observations.—Of seventy-three patients, two (nos. 16 and 41) were found to have positive reactions. One other (no. 72) exhibited an unusual phenomenon. On Dec. 3, 1921, the Wassermann reaction of the blood was negative. On July 12, 1922, just after a seizure, blood withdrawn gave a positive (4 +) reaction, as also on July 17. By July 19, the reaction was negative and remained so. This patient was under observation and underwent frequent physical examinations during the entire period and had not apparently contracted syphilis.

Comment.—Attention is called to the unusual effect of a seizure on the Wassermann reaction in one case. The only other explanations are: (1) an error in technic and (2) infection subsequent to the first test with spontaneous subsidence of virulence. The frequency with which the blood was tested and the ultimate return to negativity probably rule out both of these.

RENAL FUNCTION

PHENOLSULPHONPHTHALEIN EXCRETION

In the determination of phenolsulphonphthalein excretion, the method of Rowntree and Geraghty was used. The patient empties the bladder without the use of a catheter. He then drinks two glasses (approximately 500 cc.) of water. Phenolsulphonphthalein in the amount of 6 mg. is then injected into the buttock, and the urine collected: (1) for first appearance of color, (2) one hour after the injection and (3) two hours after the injection. The generally accepted normal limits are: (1) an excretion time of from ten to fifteen minutes, (2) an excretion of from 40 to 60 per cent during the first hour and (3) from 20 to 25 per cent during the second hour. The total for the two hours is normally from 60 to 85 per cent.

Observations.—Of thirty-three epileptic persons, fourteen (nos. 3, 9, 12, 17, 20, 24, 28, 29, 32, 45, 50, 52, 62 and 63) excreted less than 60 per cent of phenolsulphonphthalein in two hours. There was no delay in the first appearance of color.

THE TWENTY-FOUR HOUR URINE

The routine procedure was followed in the examination of the twenty-four hour specimen of urine, including total quantity, color, turbidity, reaction, specific gravity, albumin, sugar, acetone, diacetic acid and indican and microscopic examination of the centrifugated sediment. The methods employed were heat and acetic acid for albumin. Benedict's procedure for sugar, the Lange test for acetone, Gerhardt's test for diacetic acid and Obermeier's test for indican.

Observations.—Of sixty-one patients, ten (nos. 3, 7, 12, 13, 17, 32, 33, 54, 57 and 73) showed albumin or casts or both in a twenty-four hour specimen of urine. There were marked variations in the total quantity and specific gravity, probably dependent on diet and the amount of ingested fluids, the total quantity and the specific gravity being inversely proportional to one another in most cases.

URINE VOIDED IMMEDIATELY AFTER SEIZURE

The urine of three epileptic patients (nos. 8, 10 and 27) was collected immediately after seizure. Albumin and casts were present in the urine of all three and sugar in that of one (no. 27). None had shown any albumin, sugar or casts in one or more previous or subsequent interparoxysmal twenty-four hour specimens of urine.

It is interesting to note the changes in the urine of patient 27 (table 8). It will be seen that four hours after a seizure there was a marked rise in specific gravity accompanied by the appearance of albumin, sugar

TABLE 8.—*Changes in Urine of Patient 27*

Hours After Seizure	Reaction	Specific Gravity	Albumin	Sugar	Casts
¼	Acid	1.010	0	0	0
2	Acid	1.008	0	0	0
4	Acid	1.030	+	+	Hyaline and granular
24	Acid	1.004	+	0	
28	Acid	1.008	+	0	

and casts. All but the albumin had returned to the one-fourth hour state after twenty-four hours. No other abnormalities were noted.

Review of the Literature.—Novick²² and others have reported post-seizure observations. Thus, in a study of sixty patients, Novick found that two-thirds showed albumin and casts after every seizure. These constituents persisted for from twenty-four to forty-eight hours after an attack in some cases. Bisgaard²³ found marked fluctuations in the ammonia content of urine in epileptic patients due to some metabolic disturbance. This appeared to be associated with a predisposition to spasm.

FRACTIONAL URINE STUDIES (QUANTITY AND SPECIFIC GRAVITY)

The following figures are based on fractional urine studies on thirty epileptic persons over a twenty-four hour period. The method followed was patterned after that of Mosenthal. Instead, however, of starting

22. Novick, N.: The Frequency of Albuminuria with Casts in Epileptics Following Convulsive Seizures, *Arch. Neurol. & Psychiat.* 4:546 (Nov.) 1920.

23. Bisgaard, A.: Reaction of Urine in Relation to Epilepsy, *Hospitalstid.* 66:502, 1923; abstr., *J. A. M. A.* 81:1650 (Nov. 10) 1923.

day collection at 8 a. m. and night collection at 10 p. m., the hours were modified so as to conform more readily to hospital routine.

Observations.—In ten of the thirty patients (nos. 4, 24, 26, 36, 38, 48, 60, 65, 68 and 70), the total quantity of night urine exceeded 600 cc. This figure is taken as the high limit of normal because of the two additional hours of night collection by the method used as compared with that of Mosenthal. This amount is a fair average of the amounts usually passed between 7 p. m. and 7 a. m. by a healthy man on his usual diet. None of the ten patients gave evidence of renal involvement in the routine examinations of twenty-four hour urine or in the blood chemistry.

In only four patients (nos. 34, 37, 51 and 54) did fixation of specific gravity occur (i. e., variations between extremes of less than 0.009). One of these (no. 51) can be excluded because it was impossible to collect all of the two hour specimens. The specific gravity, though fixed, was high. As in all of these cases, the fluid intake was low. This observation appears to be of no significance.

INFLUENCE OF SALT-POOR DIET ON THE URINE

The effect on the blood chemistry of a salt-poor diet for seven days was shown in preceding paragraphs. The Volhard-Arnold method of determination of chloride was used.

Steyrer²⁴ gave from 6 to 22 Gm. as the normal range of sodium chloride excretion in healthy persons on a full diet. Yet thirty (nos. 3, 4, 6, 8, 10, 11, 16, 17, 19, 20, 21, 24, 25, 27, 28, 31, 33, 35, 36, 40, 48, 50, 53, 55, 57, 60, 61, 65, 69 and 70) of the fifty-four epileptic persons studied excreted more than 22 Gm. on one or more of the salt-poor days. The effect of salt restriction was generally manifested both in the reduction of the total quantity of urine and in the diminished excretion of sodium chloride. Some patients, whose excretion of sodium chloride was originally within normal limits, began to excrete in increased amounts (nos. 4, 8, 10, 11, 16, 17, 19, 33, 38, 40, 55, 60 and 61). It may be that these obtained salt in spite of all precautions. This explanation seems most likely in the cases in which the sudden increase occurred at or near the sixth day, as it was just about this time that many patients complained of being "salt-hungry." The patients (nos. 3, 7, 8, 10, 13, 17, 25, 27, 32, 33 and 57) who had shown albumin or casts in previous examinations of the urine showed no significant changes. The total amount of urine and the chloride excretion were, as is usually the case, directly proportional to one another. Some patients (nos. 7, 13, 16, 45 and 71) excreted small amounts of sodium chloride.

24. Steyrer, A.: Ueber osmotische Analyse des Harns, Beitr. z. chem. Physiol. u. Path, 2:318, 1902.

SUMMARY OF OBSERVATIONS ON RENAL FUNCTION

Taken in conjunction with the data on the blood chemistry, the following data on renal function may be given in summary.

1. A rather high percentage of epileptic persons showed a low phenolsulphonphthalein excretion without any significant changes in the values for the nitrogenous constituents of the blood.

2. Of those epileptic persons who had a high chloride content in the blood before the inception of a salt-poor diet, most showed a persistingly high content after six days. This tendency appeared for the most part in patients having a normal phenolsulphonphthalein excretion and no urinary evidence of renal disease in the interparoxysmal periods. High chlorides persisted, however, in two of three patients (nos. 8 and 10) whose urine showed albumin or casts directly after a seizure.

3. While the effect of a salt-poor diet in these epileptic persons was generally a reduction in the chlorides of the blood and urine, in a large percentage the chlorides persisted high even after six days. It is questionable whether or not this salt retention is significant. It does not appear to be connected with renal damage as gaged by present methods. Whether or not it is related to seizures will perhaps be more evident when that subject is taken up.

4. It seems that though slight and repeated renal insults may occur with each seizure it probably takes a great many years of frequent seizures to produce any serious damage. The exceptions may be patients with previously damaged kidneys. This observation is also of interest in connection with studies of blood pressure.

There appeared to be no unusual features about the fluid intake and urinary excretion in this series. There was, however, a general tendency to large fluid intake after recovery from a seizure. Individual discrepancies were probably due to errors incumbent on handling this type of patient.

OTHER OBSERVATIONS

SUGAR TOLERANCE

None of the forty-seven epileptic patients in this series had diabetes mellitus or insipidus. This knowledge was based on two or three estimations of the blood sugar during fasting, numerous examinations of the twenty-four hour urine and the clinical history. The unusual capacity for food which most of these patients possessed in the interparoxysmal periods often left the impression that perhaps this was compensatory for the period of catabolic activity represented by a seizure. Their average food requirements far exceeded those of any similar group of approximately the same size and age in any other of the hospital wards. Presumably, in any severe muscular activity, carbohydrate is most readily available and quickly burned up. Yet these patients with frequent

seizures not only did not lose weight but gained. Perhaps they had some unusual capacity for storing carbohydrate or making it out of fat or protein. This might or might not be associated with endocrine disturbance. Accordingly, an endeavor was made to ascertain how many epileptic persons could tolerate 200 Gm. of dextrose (i. e., without the appearance of sugar in the urine within two hours). This amount is from 80 to 100 Gm. more than that used in the tests based on 1.75 Gm. of dextrose per kilogram of body weight (Killian) or on the ingestion of 100 Gm. regardless of weight. The average body weight of this group (stripped) was approximately 140 pounds (63.5 Kg.).

Observations.—Of forty-seven epileptic patients, only fifteen (nos. 1, 2, 16, 19, 21, 25, 26, 31, 35, 48, 52, 53, 60, 62 and 63) excreted dextrose before the end of the two hour period. Of these, three (nos. 1, 21 and 53) showed it in only one of the eight specimens. Seven (nos. 1, 2, 16, 19, 35, 52 and 60) had previously shown a normal and two (nos. 62 and 63) a low phenolsulphonphthalein excretion. On five (nos. 21, 25, 26, 31 and 48) examinations were not done. Of the thirty-three not excreting sugar, eleven showed a low phenolsulphonphthalein elimination.

Comment.—The interpretation of these figures must be left for another part of this paper. It seems certain, however, that many epileptic patients can tolerate and store large amounts of carbohydrate. At least, it may be said that not all healthy adults of 140 pounds' weight (63.5 Kg.) can ingest 200 Gm. of dextrose without its subsequent appearance in the urine in one of the fifteen minute specimens. Moreover, the phenolsulphonphthalein test did not show a lower degree of renal impairment in those who failed to excrete sugar. This tends to rule out the occasional case of high renal threshold for dextrose associated with nephritis and hypertension.

THE SPINAL FLUID

Great difficulty was encountered in obtaining consent for lumbar puncture. Even though this procedure was left to the end of the long series of examinations, consent could be obtained from only twenty-five patients. Of these, three (nos. 5, 16 and 54) gave a positive Wassermann reaction. Patient 16 had a 4 + Wassermann reaction of the blood and was under antisyphilitic treatment at the time.

The general technic employed in carrying out the Wassermann test has been described. In the case of spinal fluid, however, the amounts were larger, and no inactivation was used.

The Lange colloidal gold test was carried out on all fluids not containing erythrocytes. The colloidal solution was prepared in the laboratory under most scrupulous conditions and was subjected to the usual

tests. Known control spinal fluids were set up each day. One patient (no. 5) who had a positive Wassermann reaction also showed a paretic type of curve.

It is interesting to compare these figures with those on the first eighty spinal fluids of nonepileptic patients submitted to the laboratory. Of these, nineteen gave a positive Wassermann reaction, while nine gave a Lange curve of syphilitic type, nine, a curve of the paretic type and one, a curve of the meningitic type. One might infer with some degree of accuracy, therefore, that syphilis of the nervous system is not present to any greater extent in epileptic patients than in patients with other nervous diseases.

No manometric studies of spinal fluid pressure were made, but there appeared to be no marked changes in pressure in any case as judged by the rapidity of drip through the lumbar puncture needle. All fluids were withdrawn during the interparoxysmal period.

Review of the Literature.—Patterson and Levi²⁵ studied the spinal fluid of fifty epileptic patients and found that the cytology, p_H , sugar, albumin, urea and chlorides were within the normal range. One patient with hyperglycemia had a parallel hyperglycorrhachia. The ninhydrin reaction was positive in a number of patients showing no other abnormality than the colloidal gold curve. Patterson and Levi also found an unusually high percentage of colloidal gold curves of the cerebrospinal syphilitic type, but it is possible that this was due to faulty technic—for example, they used only singly distilled water.

Phosphates, traces of albumin and choline (Donath) have been reported found in the epileptic spinal fluid. Dide and Sacquepee-Pellegrin produced convulsions by injecting the spinal fluid of an epileptic patient into a guinea-pig. This "hypertoxicity" was especially evident immediately after an attack. Tiburtius produced similar results by the use of brain substance triturated with serum. It is questionable whether suitable controls were used in this work.

Laures and Gascard²⁶ found a marked rise in the urea content of the cerebrospinal fluid during an epileptic seizure.

Baylac and his co-workers²⁷ observed an increase in the number of polymorphonuclears in the spinal fluid during status epilepticus. This was accompanied by a marked hemoclastic crisis.

25. Patterson, H. A., and Levi, P.: The Spinal Fluid in Epilepsy, *Arch. Neurol. & Psychiat.* **15**:353 (March) 1926.

26. Laures, G., and Gascard, E.: Urea in the Spinal Fluid in Epilepsy, *Presse méd.* **28**:396, 1920; abstr., *J. A. M. A.* **75**:509 (Aug. 14) 1920.

27. Baylac; Bize, and Stillmunkes: Polynucleosis of Cerebrospinal Fluid in Epilepsy, *Bull. et mém. Soc. méd. d. hôp. de Paris* **47**:154, 1923; abstr., *J. A. M. A.* **80**:1545 (May 26) 1923.

Comment.—The observations on the spinal fluid in the epileptic persons studied are not specific. The deviations from the norm can be accounted for by a co-existing and probably independent cause.

PROTEIN SENSITIZATION

The profound and sudden physical paroxysms into which the epileptic person is thrown were not infrequently ascribed by the patients to some food idiosyncrasy. This inference was due in many instances to the disagreeable gastric sensation constituting the aura. Clinically, the sudden change from comparative normality to a condition of violent physical distress and as sudden return to normality with little or no knowledge of what has happened suggests the liberation of some toxic substance possibly cumulative in its effects. According to present knowledge, if this is in the nature of a simple food idiosyncrasy, the most likely element at fault is protein. This does not refer to toxic split protein products, which in later investigations I found to be the basis of a widely accepted theory as to the etiology of epilepsy.

Accordingly, forty-four patients in this series were submitted to cutaneous tests, in which fifty-six of the common food and bacterial proteins were employed. The bacteria were included in an endeavor to rule out sensitiveness to some cryptogenic infection. The scratch method and tenth-normal sodium hydrate, together with proper controls, were used in each case.

The foods employed included: bluefish, egg white, egg yolk, navy bean, cheese (mixed), egg plant, cow's milk casein, egg, beef, cow's milk, corn, codfish, spinach, veal, goose feather, cat, cat hair, horse hair, chicken feather, dog hair, wheat, mustard, tea, coffee, cow's milk albumin, orange, almond, peanut, lobster, onion, mackerel, buckwheat, grapefruit, turkey, rye, tomato, salmon, chicken, white potato, lima bean, sweet potato, lamb, rice, pork and haddock.

The bacteria included: *Streptococcus nonhemolyticus*, *Pneumococcus III*, *Pneumococcus II*, *Pneumococcus I*, *Bacillus diphtheriae*, *Staphylococcus citreus*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus albus*, *Micrococcus catarrhalis* and *Staphylococcus aureus*.

Observations.—There was not a single instance of a clearcut skin reaction to any of the proteins used. Whenever there was doubt, the cutaneous was checked up by the intracutaneous method.

In the course of this work, an effort was made to detect in each of these patients a possible sensitiveness to homologous serums. For this purpose three serums were prepared from blood withdrawn from as many epileptic persons (having negative Wassermann tests), immediately after seizure. The serum of a normal person being used as a control, the serums were tested separately by both the cutaneous and the intracutaneous methods on seventy-three epileptic persons. In no

case was there any local or systemic reaction. While not conclusive, these results cast some doubt on the liberation of a peculiar protein or "toxic" substance into the blood stream during a seizure. Complement fixation tests were made in an effort to detect this substance, the antigen used being dried multiple epileptic serums. No conclusive results were recorded, but this work will bear repetition. Postseizure epileptic serum was also injected into guinea-pigs and rabbits in amounts varying from 0.5 to 5 cc., without any constant results.

Review of the Literature.—Ward and Patterson,²⁸ studying 1,000 epileptic patients at the Craig Colony and New Jersey State Village for Epileptics, reported positive reactions in 46.9 per cent, as compared with 8 per cent in 100 controls.

Howell²⁹ found all but one of eleven epileptic children sensitive to one or more food or bacterial proteins. On the other hand, Cohen and Lichtig³⁰ tested each of ten epileptic children with 128 proteins, but found no reaction which could be correlated with their convulsive seizures.

Wallis and his co-workers³¹ tested 122 epileptic patients and found that forty-six reacted to the following substances in order of frequency: peptone (twenty-eight), cereals (fifteen), fish and meat (fifteen), vegetables (nine), eggs (nine) and milk (three). The reactions of a group of 100 controls were essentially negative. These investigators selected healthy, obese, nonexcitable epileptic persons who did not respond readily to bromides. It was found that the patients were most sensitive when not fatigued and just before an attack. The sensitivity seems to vary in the same person, often disappearing after an attack.

Von Leeuwen and Leydner³² isolated a muscle-stimulating substance from the blood of epileptic patients and from cases of asthma, urticaria and migraine, which are often regarded as allergic in origin.

McCready and Ray³³ reported the cases of four patients in whom epilepsy was apparently due to a definite allergy toward food or serum protein.

28. Ward, J. F., and Patterson, H. A.: Protein Sensitization in Epilepsy, *Arch. Neurol. & Psychiat.* **17**:427 (April) 1927. This reference was found in a bibliography given at the time of the Ward-Patterson article.

29. Howell, L. P.: Differentiation of Skin Eruptions in New-Born (a study of fourteen epileptic children), *Ohio State M. J.* **19**:417, 1923.

30. Cohen, M. B., and Lichtig, H. A.: Protein Sensitization and Epilepsy, *Ohio State M. J.* **20**:571, 1924.

31. Wallis, R. L. M.; Nichol, W. D., and Craig, M.: The Importance of Protein Hypersensitivity in the Diagnosis and Treatment of a Special Group of Epileptics, *Lancet* **1**:741, 1923.

32. Von Leeuwen and Leydner, quoted by Miller, J. L.: Evidence that Idiopathic Epilepsy is a Sensitization Disease, *Am. J. M. Sc.* **168**:645, 1924.

33. McCready, E. B., and Ray, H. M.: Allergy as a Factor in the Etiology of Idiopathic Epilepsy, *M. J. & Rec. (suppl.)* **120**:117, 1924.

Crockett³⁴ reported the cases of seven epileptic persons (one definitely tuberculous) who were cured or relieved by injections of tuberculin. In three other patients there was no change. Hamilton,³⁵ Pearce,³⁶ Gudder,³⁷ Chambrelet,³⁸ Terillon,³⁹ Weir Mitchell⁴⁰ and others reported the effect of intercurrent infections and of pregnancy on epilepsy. The reports are conflicting and somewhat confusing because of inadequate follow-up data.

Others have injected epileptic serum into normal human beings and animals without producing convulsions. Ceni, however, reported rather severe reactions in epileptic persons, though sometimes a marked improvement was noticed.

Comment.—The great difficulty in the interpretation of protein sensitization studies on epileptic patients is probably due to:

1. Technic. The high percentage of positive reactions reported by some needs further corroboration.

2. Confusion of the existence of a state of allergy with the pathogenesis of epilepsy. The two conditions might well be entirely independent of each other. Moreover, few authentic cases of permanent cure (five years or over) have followed desensitization or removal of the offending protein.

3. In the case of children, figures must be regarded with some allowance for the natural hypersensitiveness of children, as pointed out by Walker,⁴¹ Rackemann,⁴² Latham and Coke⁴³ and others.

THE SPUTUM

Interparoxysmal Period.—The sputum of sixty-one epileptic patients was studied especially as to the presence of (1) tubercle bacilli, (2) unusual type of flora and (3) crystals. Other abnormalities, if present,

34. Crockett, J.: Tuberculin in Epilepsy, Brit. M. J. **1**:458, 1921.

35. Hamilton, A. S.: The Effect of Intercurrent Disorders on Pre-Existing Epilepsy, J. A. M. A. **53**:1902 (Dec. 4) 1909.

36. Pearce, F. S.: The Protein Influence of Pregnancy on Idiopathic Epilepsy, M. & S. Rep. City Hospital **76**:4, 1897.

37. Gudder: The Influence of Pregnancy on Epilepsy, J. Nerv. & Ment. Dis. **19**:65, 1892.

38. Chambrelet, J.: De l'épilepsie pendant la grossesse—son influence sur l'état de santé de l'enfant, J. de méd. de Bordeaux **29**:497, 1899.

39. Terillon: Note sur un cas d'épilepsie d'origine utérine, Ann. de gynéc. et d'obst. **16**:401, 1881.

40. Mitchell, Weir, quoted by Hamilton (footnote 35).

41. Walker, quoted by Longcope, W. T.: Anti-Anaphylaxis and Desensitization, Physiol. Rev. **3**:240, 1923.

42. Rackemann, F. M.: A Clinical Study of One Hundred and Fifty Cases of Bronchial Asthma, Arch. Int. Med. **22**:517 (Oct.) 1918.

43. Latham, A., and Coke, F.: Sensitization in 270 Cases of Asthma, Practitioner **109**:121, 1922.

were noted. The procedure adopted was to examine three or more early morning specimens that were received at the laboratory before 9 a. m. In a few instances only one specimen was obtained. The Ziehl-Neelsen method was used for the detection of tubercle bacilli. Under flora, the "usual type" refers to the organisms seen in the smear stained for tubercle bacilli and includes such forms as pneumococci, streptococci, staphylococci and occasionally *Micrococcus tetragenus*. As these organisms were identified morphologically, no attempt was made to ascertain anything other than the predominance or exclusive presence of any one type.

Paroxysmal Period.—An attempt was made to ascertain whether the profuse salivation during a paroxysm was purely a nervous phenomenon or an attempt to rid the body of some toxic substance. The sputum of ten different epileptic patients was collected during and immediately after a paroxysm. After filtration through a Berkefeld filter, a 1 cc. sample of each sputum was injected subcutaneously into a healthy guinea-pig weighing approximately 250 Gm. In no instance was there any local or systemic reaction within twenty-four hours. The experiment was repeated in most instances with unsterile, unfiltered sputum, with like results. A batch of grouped filtered sputums was made up, and intracutaneous inoculations were made in twenty-five epileptic patients, including those who had furnished the specimens. No reaction was obtained.

Summary.—No tubercle bacilli or other abnormal elements were found in the sputums of sixty-one epileptic patients. The detection of a toxic substance by the biologic method was unsuccessful, but the limited number of experiments warrants further study.

Comment.—The negativity of these observations is of interest in a consideration of the bacterial and toxic theories as to the causation of the epileptic fit.

THE FECES

Casual fecal specimens of sixty epileptic patients were examined. There were no restrictions as to diet. The benzydine and guaiacum tests were used for occult blood, and the results recorded as positive when both tests agreed. The simple emulsion in saline solution and the salt saturation methods were used for the detection of ova. The usual technic for food digestion was followed, described under the Schmidt diet in subsequent paragraphs. Estimation of the predominating flora was made by simple smear and Gram's stain. The types of gram-positive organisms (spore-bearers, streptococci, etc.) were not recorded. The following outline covers the general procedure:

1. Gross examination of feces: Amount, color, odor, consistence, reaction, mucus, pus, blood, tissue fragments, calculi, bile, parasites.

2. Chemical examination: Benzidine, guaiacum and bichloride tests.

3. Microscopic examination: Protein, fat, carbohydrate digestion, ova, yeasts, molds, *Sarcinae*, crystals, tissue elements, flora.

Color.—Three patients (nos. 34, 60 and 64) had stools of an unusual color: two, black and one, reddish brown. The latter (no. 64) owed the color to the presence of gross blood apparently associated with hemorrhoids.

Consistence.—Twenty-three patients had a hard, constipated type of stool, while seven had fluid feces (i. e., small solid particles floating in an abundance of fluid).

Reaction.—All specimens were amphoteric to litmus.

Gross Blood.—In one specimen only (that of no. 64) was gross blood evident.

Occult Blood.—Although present in many, occult blood was of no significance because of the meat-containing diet. Yet it is interesting to note how many patients on a similar diet gave negative benzidine and guaiacum tests.

Ova and Parasites.—All specimens were negative for ova and parasites.

Food Digestion.—There were seven persons (nos. 22, 23, 49, 55, 57, 61 and 62) with poor protein digestion, as evidenced by the presence of many intact, well striated voluntary muscle fibers. The report of this observation may be open to criticism. It has been my experience, however, that the stools of a healthy person without dietary restrictions rarely shows more than an occasional well striated muscle fiber, unless the meat has been poorly chewed or ingested in excess. Moreover, many of the epileptic persons studied have stated that they feel distinctly better on a meat-free diet.

Flora.—As the reports were based merely on morphology, no definite conclusions were reached.

*Digestive Power of the Intestine.*⁴⁴—The technic of Schmidt was followed in the tests for digestive power of the intestine and a specimen of the stools collected after seventy-two hours. On the iodine (carbohydrate) and acetic acid (fatty acids) slides, it was sometimes difficult to judge accurately as to the efficacy of digestive power. These cases were marked "fair."

After three days of the Schmidt-Strasburger diet, two of twenty-three patients (nos. 8 and 27) showed 30 per cent of gas formation by the twenty-four hour fermentation test, an observation that suggests

44. Schmidt and Strasburger: *Die Faeces der Menschen*, Berlin, A. Hirschwald, 1901. Schmidt: *Die Funktionsprüfung des Darmes*, Munich, J. F. Bergmann, 1904.

imperfect intestinal digestion. One patient (no. 21) showed poor digestive capacity for protein. The casual stools of patients 8 and 21 had previously been classified as abnormal.

Summary.—In all, twelve specimens of stools were classified as abnormal, based on color, consistence, the presence of blood or evidence of faulty food digestion.

Review of the Literature.—Cobb,⁴⁵ studying the fecal acidity of fifty epileptic girls and women, found a mean acidity of 5.22 (in terms of normal sodium hydrate necessary to neutralize the acids extracted from 100 Gm. of feces). This figure was subject to much variation in individual cases and had no relation to the number of paroxysms.

Comment.—Many epileptic patients, probably of a certain type, appear to be benefited by colonic eliminative measures or dietary limitations or both. The abnormal fecal observations in this series may point, in these selected cases, to the bowel as a contributory factor in the pathogenesis. While the constipated patients felt better after catharsis, there was no appreciable effect on the frequency of seizures.

CARDIAC FUNCTION ⁴⁶

The procedure followed in the test of fifty-eight epileptic persons for cardiac function was as follows: The blood pressure, pulse and heart were examined under restful conditions. The patient then hopped fifty times, and the pulse and heart were reexamined.

Pulse Rate.—Five patients (nos. 4, 5, 10, 26 and 45) had a pulse rate of 64 or less, suggesting a vagotonic state. This list was later supplemented by eight additional patients (nos. 6, 9, 20, 27, 28, 30, 60 and 61), making a total of thirteen who showed bradycardia. The bradycardia in one patient (no. 26) was accompanied by a marked sinus arrhythmia. One patient (no. 39) had a persistent pulse rate of from 120 to 124. The exercise tolerance in nearly every case was good, there being only a slight increase in the pulse rate (patients 55 and 68 being the exceptions).

Cardiac Abnormalities.—Eleven patients exhibited deviations from the norm; one (no. 55) showed mitral stenosis; two (nos. 31 and 40), mitral insufficiency; two (nos. 26 and 69), bradycardia and sinus arrhythmia (vago-tonia); one (no. 4), reduplication of the second pulmonic sound and cardiac hypertrophy; one (no. 2), accentuation of the second aortic sound; one (no. 18), aortic dilatation, and three (nos. 36, 48 and 68), neurocirculatory asthenia.

45. Cobb, G.: The Fecal Acidity in the Insane Epileptic, J. Ment. Sc. **72**:83, 1926.

46. Dr. Hubert Mann gave careful attention to these studies.

Electrocardiographic Observations.—Left ventricular predominance was shown in seven patients (nos. 13, 16, 31, 35, 44, 62 and 63); right ventricular predominance in one (no. 7), and extrasystole in two (nos. 19 and 24). Of these, patient 31 had a mitral insufficiency.

Comment.—The general freedom from organic cardiac defects is surprising in view of the repeated cardiovascular strains to which the epileptic person is subjected during a paroxysm.

THE BLOOD PRESSURE

Diurnal Variations.—Records of blood pressure were made for twenty-nine epileptic patients during their usual daily hospital life, the blood pressures being taken before and after each meal, and on seizure-free days only. The first reading of blood pressure was done approximately one-half hour after the patient's rising, following the usual morning ablution and dressing.

From these rather meager records it was noted that the usual slight rises occurred in the afternoon, evening and after meals. In this respect there is no variation from the physiologic. Readings that were started but discontinued because of the occurrence of a paroxysm later in the day showed no essential changes, except when, by chance, they were taken just before a fit. In the latter case, the pressure was usually high (no. 24). Hourly studies during the waking period sometimes showed surprising variations (no. 2). One patient (no. 73) had severe nephritis of the arteriosclerotic type and also had what was apparently essential epilepsy.

Postseizure Variations.—Estimations of blood pressure were made on twenty-two epileptic patients immediately following seizure. As a basis for comparison, the average normal blood pressure of each patient is taken into consideration. In cases in which a rise occurred, readings were taken every five minutes until the return to the average normal figure. Five minute intervals were found sufficient, as minute readings (the cuff being left in place) gave essentially a repetition of the same pressure level.

It was found that in about one half of the patients studied the blood pressure returned to normal within fifteen minutes. One might say that this constituted an excellent clinical test for cardiac function. A few patients (nos. 4, 35, 47, 48, 68 and 71) exhibited slight if any rise in pressure. Others (nos. 65 and 67) had a prolonged elevated level from 106 systolic and 72 diastolic to 170 systolic and 136 diastolic (no. 65) and from 110 systolic and 70 diastolic to 164 systolic and 112 diastolic (no. 67). One patient (no. 63), whose temperature, pulse and respiration had been taken one-half hour before the seizure, showed no appreciable increase in the rectal temperature and a slight increase in the

pulse and respiration rates. Another patient (no. 52) had a normal blood pressure of 110 systolic and 80 diastolic just before a seizure.

In general, it might be said that the increase in blood pressure was proportional to the number and severity of the seizures. It would seem, therefore, that the rise was due at least in part to muscular exertion. That this is not the sole explanation will be evident from data submitted in connection with petit mal attacks.

Review of the Literature.—Addis⁴⁷ observed variations in blood pressure on normal soldiers of approximately the same age as the epileptic persons studied in this paper (from 21 to 31). Comparing the basal state, that found after an all night sleep and before breakfast or exercise, to the day state, he observed that the basal norm of seventy-six persons was 99 systolic and 71 diastolic, with a pulse rate of 63, and that the day norm of 300 persons was 127 systolic and 78 diastolic, with a pulse rate of 80.

Studying the effects of food, exercise and excitement, the same author concluded that food has little or no effect. Exercise in the form of 100 hops raised the systolic pressure from 125 to 156, the rise being most marked during the first period. The degree of change is proportionate to the level existing before exercise. My figures on epileptic patients in the postparoxysmal state show that the highest pressure is attained within the first five or ten minutes.

Brooks and Carroll,⁴⁸ studying three groups of patients with average basic afternoon systolic pressures of 142.5, 100 and 204.5, found that in relation to sleep, the greatest drop occurs within the first two hours. The greater the basic level, the greater is the drop. After the second hour, the pressure gradually rises. Tarchanoff⁴⁹ had previously obtained similar results in young dogs, and Brush and Fayerweather⁵⁰ in normal man.

Pollock and Treadway⁵¹ studied forty-one epileptic patients of whom eighteen had systolic pressures of 120 or below and twenty-three, from 125 to 200. Of seventeen patients examined on the day of convulsion, seven had a systolic pressure above 135, and ten, below 120. The pulse pressure in all but eight patients varied between 40 and 50 mm. Of the

47. Addis, T.: Blood Pressure and Pulse Rate Levels: First Paper, Arch. Int. Med. **29**:539 (April) 1922; Second Paper, *ibid.* **30**:240 (Aug.) 1922.

48. Brooks, H., and Carroll, J. H.: A Clinical Study of the Effects of Sleep and Rest on Blood Pressure, Arch. Int. Med. **10**:97 (Aug.) 1912.

49. Tarchanoff, J.: Quelques observations sur le sommeil normal, Arch. ital. de biol. **21**:318, 1894.

50. Brush, C. E., and Fayerweather, R.: Observations on the Changes in Blood Pressure During Normal Sleep, Am. J. Physiol. **5**:199, 1901.

51. Pollock, L. J., and Treadway, W. L.: A Study of Respiration and Circulation in Epilepsy, Arch. Int. Med. **11**:445 (April) 1913.

eight with pulse pressure above 55 mm., five either were measured on the day of convulsion or had some cardiovascular disease. Many patients exhibited Traube-Hering waves, especially just preceding or following a fit and usually disappearing by the fifth day. The sequence of events leading up to a convulsion seemed to be a preliminary rise in blood pressure followed by a sudden drop, then a period of apnea followed by the fit. In the patients with petit mal and some with grand mal types of epilepsy, the blood pressure was low. During the convulsive period, the pulse was uniformly rapid.

With a view to a critical interpretation of the variations in blood pressure mentioned, it is interesting to note the observations of Alvarez⁵² in 15,000 university freshmen. Among the men (6,000), he found a tension of more than 130 mm. of mercury in about 45 per cent, and of more than 140 mm. in 22 per cent. Among the women, 12 per cent had tensions exceeding 130 mm. and 2 per cent, exceeding 140. The pressures for men were grouped around 127 mm. at the age of 16, and around 118 at the age of 30. The pressures for women varied from 118 mm. at the age of 16 to 111 at 24 and 117 at 40 years.

Comment.—The interpretation of the variations in the blood pressure of the epileptic patient can be properly made only after due consideration of the variations in normal persons of the same age and sex. The only patient (no. 73) who had a persistent hypertension had an advanced cardiorenal condition to explain it. One can state with some certainty that the degree of rise in pressure, properly considered, is an indication of the physical severity of the fit. Compared with Addis' figures on the normal soldier, the rise in the epileptic patient is more than that produced by 100 hops of a normal adult man (31 mm.). This is probably not as significant as the fact that in a few exceptions there was little or no increase in pressure (nos. 4, 35, 47, 48, 68, 70 and 71). It is important to know why these patients showed no appreciable variation after a grand mal attack. Looking back on their tests for cardiac function one sees that patient 4 had bradycardia but fairly good tolerance of exercise; patient 35 had fair tolerance; patient 47 was normal; patient 48 had mild neurocirculatory asthenia; patient 68 had distinctly poor tolerance with an initial pulse rate of 100, and patients 70 and 71 were normal. Incidentally, patients 70, 68, 35 and 4 had some auscultatory cardiac signs which, at the time of examination, did not appear to be definitely due to organic disease.

The basal morning pressures and pulse rates in epileptic patients are comparable with those of Addis for the norm, except for the relatively high percentage of bradycardia in the epileptic patients. The occurrence

52. Alvarez, W. C.: Blood Pressures in Fifteen Thousand University Freshmen, *Arch. Int. Med.* **32**:17 (July) 1923.

of a temporary heart block in the epileptic patient will be considered under pathologic studies. The effects of rest and exercise on the epileptic patient are essentially those on the normal man.

BASAL METABOLIC RATE

The Benedict type of machine (Sanborn) was used in the estimation of the basal metabolic rate (by indirect calorimetry). Basal conditions included fourteen hours of rest and abstinence from food plus one-half hour rest on the metabolism couch just before the test. The rectal temperature taken just before the rest period was normal in each instance. A separate room, remote from the wards and laboratory proper, was utilized. Ten minute readings with one minute checks served as an index to the reliability of a single test. All abnormal rates and obviously unreliable readings were rechecked by a second test.

Observations.—Six patients (nos. 3, 4, 35, 60, 61 and 62) showed abnormally high basal metabolic rates ($+15$ per cent or above). One of these patients (no. 4) had a persistent hyperpnea each time he underwent a test. It is interesting to note that eight patients (nos. 6, 9, 20, 27, 28, 30, 60 and 61) had definite bradycardia before the test, which was completed between 9 and 10 a. m. One (no. 6) had a pulse rate of 48 before the procedure began and 56 at its termination. Seven patients (nos. 1, 6, 17, 27, 39, 60 and 61) had respiratory rates of 14 or below. Four of them (nos. 6, 27, 60 and 61) also had bradycardia, although two (nos. 60 and 61) had moderately high metabolic rates.

As a basis for comparison, the first 250 patients (other than epileptic patients included in this paper) sent to the laboratory for a basal metabolic test were classified according to the diagnoses at discharge. It was found that there was a considerably lower percentage of high basal rates among the epileptic persons.

Review of the Literature.—Talbot and his co-workers⁵³ studied eleven children affected with idiopathic epilepsy and found the metabolic rate normal or elevated in all. Bornstein⁵⁴ reported a marked increase in metabolic rate after an epileptic attack, the increase remaining for twenty-four hours. Talbot and his co-workers found no evidence to support this contention. Bowman and Grabfield⁵⁵ found the metabolic rate to be from -20 to -21 per cent in three epileptic patients and normal in three others. No psychosis was present.

53. Talbot, F. R.; Hendry, M., and Moriarty, M.: The Basal Metabolism of Children with Idiopathic Epilepsy, *Am. J. Dis. Child.* 28:419 (Oct.) 1924.

54. Bornstein, A.: Untersuchungen über die Atmung der Geisteskranken, *Monatschr. f. Psychiat. u. Neurol.* 24:392, 1908.

55. Bowman, K. M., and Grabfield, G. P.: Basal Metabolism in Mental Disease, *Arch. Neurol. & Psychiat.* 9:358 (March) 1923.

ROENTGENOGRAPHIC STUDIES IN EPILEPSY⁵⁶

The Skull.—For the sixty epileptic patients, the procedure included the making of lateral and anteroposterior views of the skull on stereoscopic plates. For the lateral views, a 5 inch spark gap, 30 ma. and 26 inch distance from target to plate were used. The time of exposure in seconds corresponded to the interparietal measurement of the skull in inches. In the first exposure, the central ray was directed through a point 1 inch (2.5 cm.) anterior to the external auditory meatus. A second plate was made after the tube had been shifted 2½ inches (6.27 cm.) caudad and 15 degrees cephalad. For the anteroposterior views, a 5½ inch spark gap, 30 ma. and 26 inch distance from target to plate were used. With the nose and forehead of the patient on the table, the central ray was directed at the nasion. The time of exposure in seconds was one and a half times the distance in inches between theinion and the nasion. No intensifying screens were used.

For the 100 controls, the procedure included only lateral views. A 5 inch spark gap, 30 ma. and 84 inch distance were used, the central ray being directed at a point 1 inch (2.5 cm.) anterior to the external auditory meatus. The time of exposure in seconds corresponded to the interparietal distance in inches. Double intensifying screens were used.

The proper interpretation of a picture of the skull depends on (1) the technic employed and (2) the normal anatomic hindrances (i. e., overlapping of structures) and a thorough knowledge of the normal for a particular age and sex. As a guide in the proper interpretation of the anomalies in the skulls of epileptic patients, therefore, the skulls of 100 normal persons of approximately the same age as the epileptic patients were studied. The series of normal persons included doctors, attendants and patients without any known physical or mental disability, except as stated.

The anomalous observations in the skulls of the sixty epileptic patients may be classified from an anatomicopathologic standpoint as in table 9. Of sixty patients, forty-three showed what, at the time the pictures were taken, were considered departures from the usually accepted anatomic norms. After the work was completed, however, this opinion was modified by reason of the results obtained with the 100 normal subjects. Calcification or separation of the suture lines, slight irregularities in contour of the inner table, depressions, prominent diploe and calcification of the pineal body were among the unusual features noted. In five cases, the anatomic changes were apparently associated with a long standing injury of the head without subsequent epilepsy.

56. Dr. Frank Liberson gave scrupulous attention to this part of the work. The control studies were made entirely at his expense.

There was considerable variation in the size of the sella and the interclinoid space (as measured between the middle and posterior clinoids). The sella turcica varied from 6 by 4 by 9 mm. to 14.5 by 8 by 11 mm., the figures referring to length by depth by height. The interclinoid space varied from 0 to 10 mm., the former figure indicating no visible space, but not necessarily fusion of the bony processes.

Other Structures.—In fifty-five epileptics the thorax was studied. Of these, eighteen showed evidence of an active or healed pleuritic or pulmonary lesion. The latter in five or six instances (nos. 13, 17, 27, 45, 48 and 61) was distinctly tuberculous. Of thirty-five patients, one (no. 26) had a decided enlargement of one lobe of the thyroid gland. Of thirty-five patients, one (no. 26) showed evidence of a persistent thymus. Of fifty-nine patients, thirty displayed a definite dental patho-

TABLE 9.—*Anatomicopathologic Classification of Anomalies Encountered in Skulls of Epileptic Patients*

Anomaly	Patients
Increase in convolucional markings (nos. 3, 9, 10, 34 and 45).....	5
Areas of increased density, of doubtful etiology (nos. 3, 5, 29, 37, 40, 43, 44, 51 and 63).....	9
Areas of diminished density, of doubtful etiology (nos. 1, 12, 54 and 60).....	4
Bridging of clinoids (nos. 6, 9, 13, 32, 39, 49 and 52).....	7
Female type of skull (nos. 11, 13 and 40).....	3
Aeromegalie type of skull (nos. 9 and 65).....	2
Brachiocephalie type of skull (no. 12).....	1
Dolichocephalie type of skull (no. 60).....	1
Syphilitic skull (nos. 3, 18 and 58).....	3
Traumatic changes: hiatus or exostosis (nos. 5, 7, 13, 16, 20, 43, 57, 61, 67 and 70).....	10
Evidence of increased intracranial pressure (nos. 7, 9, 10, 34, 57 and 62).....	6
Calcification of pituitary gland (no. 25).....	1
Pituitary tumor (no. 39).....	1
Irregularity of internal table (nos. 47 and 52).....	2
Irregularity of external table (no. 57).....	1
Cerebral endothelioma (no. 62).....	1

logic condition. This consisted chiefly of retained root and periapical abscess. Of thirty-six patients, two (nos. 1 and 27) showed an atrophic or undeveloped condition of one or both testicles. Examination of the gastro-intestinal tract was made in two patients (nos. 17 and 20) in whom there appeared to be some derangement, but no abnormal roentgenographic evidence was obtained. In one patient (no. 73), calcified flakes were found in the left and right posterior tibial arteries. The tracheal, radial and cerebral blood vessels showed no calcified deposits. This man had a marked generalized atherosclerosis.

Summary.—Deviations from the generally accepted anatomic appearance of the skull were found in forty-three of the sixty epileptic patients studied. In view of the surprising number of similar changes in many of the skulls of 100 normal persons, a definite opinion as to their clinical significance is unwarranted. The anthropologic types, the syphilitic skull, the traumatic skull, the pituitary tumor and the dural endothelioma are definite. These comprise twenty-two instances. The

morphologic variants (in seven patients) are suggestive only when taken in conjunction with other evidence. Epilepsy in the twelve patients with the traumatic or neoplastic type of skull could not in all instances be attributed to the lesion detected. Not infrequently, the pathologic changes were subsequent to the onset of the epilepsy. In other words, a man may have an old fracture or hiatus of the skull and epilepsy but both conditions be unrelated. Of the three patients with syphilitic skulls, two (nos. 18 and 58) had had negative results in serologic tests and one (no. 58) a negative result in the Wassermann test of the spinal fluid and a negative colloidal gold curve. Of the epileptic patients with positive results in serologic tests (nos. 16, 41 and 72), one (no. 16) showed some change in the skull; patient 72 was not studied. Three epileptic patients (nos. 3, 16 and 54) with positive results in tests of the spinal fluids all showed some changes in the skull. In no instance, however, was a definite diagnosis of syphilis made roentgenologically.

Review of the Literature.—The literature concerning the roentgenologic appearance of the skull in epilepsy centers attention chiefly about the bony structures in the region of the pituitary body. Schüller⁵⁷ stated that an intrasellar tumor is suggested by a widening and deepening of the sella, a thinning of the floor and a thinning, backward displacement and inclination of the dorsum which forms an acute angle with the planum sphenoidale. There is evidence of acromegalic change in the rest of the skull (thickening of the wall, bony ridges and enlargement of the pneumatic spaces). He also called attention to a localized thickening of the base of the skull and the frontal floor in epilepsy. Johnston,⁵⁸ in a study of 100 epileptic patients between the ages of 15 and 35, called attention to: (1) an overgrowth of the anterior and especially of the posterior clinoids, which are folded over and down on the pituitary gland; (2) a decided difference in the size of the pituitary fossa and gland; (3) a fossa largely or completely roofed over, the clinoids sometimes overlapping, and (4) an increased density of the bony structure forming the roof of the orbits, sphenoidal sinus and ethmoidal cells. The sphenoidal cells may be blocked with newly formed bone tissue. McKennan described as "local acromegaly" a hyperostosis of the clinoid processes, anterior fossa and sometimes the postclinoidal region. The plates of normal and acromegalic persons do not show these changes.

57. Schüller, A.: *Roentgen Diagnosis of Diseases of the Head*, Translation, St. Louis, C. V. Mosby Company, 1918.

58. Johnston, G. C.: *The Radiography of the Pituitary in Its Relation to Epilepsy*, *Am. J. Roentgenol. (n.s.)* 1:172, 1914.

McKenna and his co-workers⁵⁹ believed that the frequency of attacks is more important than the duration of the epilepsy in the production of these bony changes. Timme⁶⁰ was of the opinion that roentgenographic changes in the sella are not indicative of a pituitary lesion. Munson and Shaw⁶¹ found inconstant anatomic changes in the pituitary. Moreover, the former⁶² investigated the sella turcica in autopsies of eighty-five unselected epileptic patients and found it varying greatly. While roofing may be present in the x-ray picture, the gland post mortem appears to be well exposed and free from pressure. The bony changes are such as might be seen in nonepileptic persons. Lissner and Nixon⁶³ reported six cases of epilepsy associated with dyspituitarism. Except for one patient who was distinctly acromegalic, the x-ray pictures of the skull were normal. Camp⁶⁴ pointed out the difficulties involved in the roentgenologic interpretation of pictures of the sella. Variations in the shape of the clinoids, union between them and bridging are apparently of no significance. Anton,⁶⁵ in a study of fifteen epileptic patients, described a relative hypertrophy of the cerebellum, which can be readily recognized in x-ray plates.

As to the relationship of dental pathology to epilepsy, Tracy⁶⁶ and Tholuck⁶⁷ were convinced of this possibility.

Harryman and Donaldson⁶⁸ studied the gastro-intestinal tract in 125 epileptic patients roentgenologically and found hypermotility of the large bowel in 50 per cent and normal motility in the remainder.

Comment.—The results of these detailed studies of the skulls of epileptic patients, as compared with the skulls of normal persons of the same age and sex, reveal a high proportion of pathologic conditions. The

59. McKenna, T. M. T.; Johnston, G. C., and Henninger, H.: Observations on Epileptics Chiefly from an X-Ray Standpoint, *J. Nerv. & Ment. Dis.* **41**:495, 1914.

60. Timme, W.: Clinical Features Accompanying Changes in the Sella Turcica, *Arch. Neurol. & Psychiat.* **2**:240 (Aug.) 1919; *Arch. Ophth.* **49**:268, 1920.

61. Munson, J. F., and Shaw, A. L.: The Pituitary Gland in Epileptics, *Arch. Int. Med.* **14**:393 (Sept.) 1914.

62. Munson, J. F.: The Pituitary Gland in Epileptics, *Arch. Int. Med.* **21**:531 (April) 1918.

63. Lissner, H., and Nixon, C. E.: Dyspituitarism and Epilepsy: A Report of Six Cases, *M. Clin. North America* **6**:1471, 1923.

64. Camp, J. D.: The Sella Turcica, Significance of Changes in Its Roentgenographic Appearance, *J. A. M. A.* **86**:164 (Jan. 16) 1926.

65. Anton, G.: Roentgenography of the Head in Epilepsy, *Jahrb. f. Kinderh.* **93**:69, 1920; abstr., *J. A. M. A.* **75**:1603 (Dec. 4) 1920.

66. Tracy, E. A.: Teeth Anomalies and Epilepsy, *Dental Cosmos* **69**:410, 1927.

67. Tholuck, H. J.: Dentistry in Epilepsy, *München. med. Wchnschr.* **70**:1199, 1923; abstr., *J. A. M. A.* **81**:1994 (Dec. 8) 1923.

68. Harryman, W. W., and Donaldson, S. W.: Radiologic Gastro-Intestinal Studies in Epilepsy, *J. A. M. A.* **81**:813 (Sept. 8) 1923.

uniformly unsatisfactory postmortem examination of the head may possibly be discounted by closer attention to roentgenographic detail during life. The question of pituitary epilepsy cannot be settled by roentgenographic studies alone. The technic and interpretation are subject to too much error. I have yet to see in my routine postmortem work a pituitary body encroached on by bony structure, except in the case of fractures of the base or, indirectly, when the pituitary itself is the seat of change. In his experimental work, Cushing produced epileptic convulsions in animals by means of partial hypophysectomy with its associated secretory insufficiency. Similar conditions in man have been reported in connection with epilepsy, some patients even having gustatory attacks referable to direct pressure of the pituitary on the adjacent uncinate cortex. The anatomic aspects of this little structure certainly make theories involving pressure seem plausible. Encased in a bony recess covered over by tough, unyielding dura, the gland and its intercavernous sinuses need little interference to cause malfunction. The larger anterior lobe is glandular and richly vascularized, while the posterior is small, nervous in structure and connected with the infundibulum and third ventricle. The highly complex nature of the pituitary suggests that slight changes are more likely to manifest themselves in other ways than by convulsions. At least, there is no justification for the assumption that it is responsible for more than a small proportion of epilepsies.

Again it is suggested that from an etiologic standpoint, there are many different conditions included under the term "epilepsy."

STUDIES OF THE SYMPATHETIC NERVOUS SYSTEM

The clinical phenomena seen in epilepsy seem to indicate that in its objective manifestations, at least, this disease is essentially a disturbance of the nervous system. Aside from evident gross lesions in the sensory or motor areas of the cortex or their respective pathways, there seems to be some evidence that the sympathetic nervous system is involved in one group of cases at present classified together with other types under the general term "epilepsy." There is probably a close relationship of this system to at least two of the ductless glands, the suprarenal and thyroid glands. Together, they provide a delicately balanced, highly sensitive mechanism capable of producing many of the peculiar physical and mental phenomena noted in epilepsy.

The sympathetic (vegetative) nervous system may be divided into:

1. The sympathetic proper, the fibers of which arise in the intermediolateral regions of the cord, passing out by the anterior roots to end in ganglions which send fibers to the smooth muscle, heart, blood vessels, secretory glands, etc. The afferent fibers conduct visceral sensations and referred visceral pain. The ganglions form a series in front of the vertebral column, one on either side.

2. The autonomic system or system of the extended vagus. The most important constituent is the vagus nerve. In the craniobulbar portion, fibers pass to the ciliary ganglion (constricting the pupil), secretory fibers to the submaxillary gland, stomach and intestines, inhibitory fibers to the heart, constrictors to the bronchi and motor fibers to the esophagus, stomach and intestines. In the sacral portion, fibers supply the descending colon, rectum, anus, bladder and genital system by way of the pelvic nerve. The autonomic ganglions are placed more peripherally than those of the sympathetic proper.

The entire sympathetic nervous system has three plexuses: cardiac, solar and hypogastric, which receive fibers from both the divisions described.

Physiologic evidence points to the maintenance of a constant balance between the sympathetic proper and the autonomic system during health. An imbalance manifests itself as an overactivity of the one or the other system, and these conditions are at present defined by the generally accepted terms "sympatheticotonia and vagotonia."

The clinical signs pointing to vagotonia are small pupils, salivation, flushing, sweating, clammy hands and feet, dermatographia, bradycardia, irregularity of respiration, bronchial asthma, hyperacidity, cardiospasm and pylorospasm, spastic constipation and sphincter contraction. Eosinophilia, pharyngeal anesthesia, respiratory arrhythmia, angina, tremor and urinary frequency may be present. Sympatheticotonia is characterized by dilated pupils, prominence of the eyes, dryness of the mouth and skin, tachycardia and alimentary glycosuria. Loss of hair and unexplained rises in temperature may occur.

The work of Eppinger and Hess and others has shown that when both systems supply the same structure their action is antagonistic. Thus, the sympathetic dilates the pupil, increases the heart rate and inhibits movements of the gastro-intestinal tract, an influence directly opposed to that of the autonomic system. Moreover, an increased tone in one system practically rules out an increased tone in the other. Thus, patients who are sensitive to pilocarpine are less sensitive to epinephrine.

In the experimental study of thirty-seven epileptic patients, I attempted to supplement the clinical features suggestive of sympathetic imbalance by observations of the effects of the so-called "sympathetic" drugs. Epinephrine (8 minims of 1:1,000 solution) stimulates the sympathetic system proper, causing tremor, rigor, sense of cold, polyuria, glycosuria and a rise in blood pressure. Pilocarpine ($\frac{1}{8}$ grain) stimulates the autonomic system, causing salivation, nausea, sweating, flushing and fall in blood pressure. Atropine ($\frac{1}{100}$ grain) paralyzes the autonomic system, as evidenced by dryness of the mouth and throat, palpitation and oppression. The dosage decided on in the study was the

smallest consistent with a slight response in a normal man, weighing approximately 65 kilograms. Those who were excessively stimulated by the epinephrine or pilocarpine were considered tentatively as belonging to the sympatheticotonic or vagotonic group.

It is expedient to consider the effects of all three drugs together (pilocarpine and atropine, as vagotonic stimulant and paralyzant, respectively; epinephrine as a sympathetic stimulant). These observations were recorded without any reference to the clinical status of the patient. The results may be tabulated as follows:

Observations.—Eighteen patients (nos. 5, 7, 13, 17, 20, 24, 25, 27, 29, 31, 32, 39, 40, 45, 47, 50, 63 and 68) manifested an excessive response to pilocarpine, as displayed by salivation (50 cc. or more), perspiration, lowered blood pressure or bradycardia. Of these, two (nos. 25 and 27) were borderline cases. Six (nos. 20, 24, 31, 32, 47 and 50) also exhibited a response to epinephrine. Of the vagotonic types enumerated, fifteen (nos. 5, 13, 20, 24, 25, 27, 29, 31, 32, 39, 40, 45, 47, 50 and 63) gave no evidence of reaction to atropine, thus suggesting a fair degree of vagotonicity.

Excessive response to epinephrine, as displayed by tremor, polyuria or rise in blood pressure, occurred in twenty-two patients (nos. 2, 6, 10, 11, 20, 21, 22, 24, 26, 31, 32, 34, 35, 36, 47, 50, 58, 60, 62, 65, 69 and 71). Three were deemed to be doubtful (nos. 60, 65 and 69). Of the twenty-two patients, six (nos. 20, 24, 31, 32, 47 and 50) also gave an excessive response to pilocarpine. Six (nos. 2, 26, 31, 35, 60 and 62) showed an alimentary glycosuria during the sugar tolerance tests also suggestive of sympatheticotonia. Three (nos. 35, 60 and 62) also had an increased basal metabolic rate.

Of the vagotonic types, clinical evidence, mainly in the form of bradycardia and sinus arrhythmia, supported the laboratory results on only five patients (nos. 5, 7, 13, 24 and 45). Only two of the sympatheticotonic types had clinical support for the laboratory data (nos. 6 and 20).

Review of the Literature.—Popea and his co-workers⁶⁹ studied the rôle of vagotonia in forty-five epileptic patients. By paralyzing the vagus with atropine, seizures were produced after ten minutes in six persons. In sixteen other persons, convulsions occurred within twelve hours. These authors concluded that an epileptic seizure may be accompanied or even preceded by hypervagotonia, but that the latter is not a causative factor.

69. Popea, A.; Eustatziu, G., and Holban, G.: Rôle of Hypervagotonia in the Epileptic Seizure, *Compt. rend. Soc. de biol.* **92**:1170, 1925; abstr., *J. A. M. A.* **85**:73 (July 4) 1925.

Tinel⁷⁰ likened the epileptic paroxysm to a state of sensitiveness or hypervagotonia, as shown by the presence of alimentary disturbance and increased oculocardiac reflex. During the quiescent period, a hypervagotonia or sympatheticotonia may exist.

Comment.—Clinical evidence favored an existing abnormal state of vegetative nervous system in only seven patients. Laboratory studies raised the number to thirty-five or forty (five being doubtful) out of a total of eighty on whom tests were made (on thirty-three with pilocarpine; on forty-seven with epinephrine). Approximately one half of the patients tested were either sympatheticotonic or vagotonic. Six patients responded to both types of drug stimulants. The prodromal and post-seizure signs and symptoms of an epileptic paroxysm include many of those characteristic of hypervagotonia. In many instances, however, the interparoxysmal period is characterized by a hypersympatheticotonic state. Thus, clinical observations are not at all inconsistent with the laboratory observations. A delicate balance is maintained by the antagonistic action of the autonomic (vagotonic) and sympathetic systems at the most quiescent or normal intervals of the interparoxysmal stage. At unknown intervals preceding and following a seizure, this balance seems to be disturbed and one system of the other predominates its action. It is not unlike a delicately adjusted thermostat that suddenly gets out of order. This state in the epileptic might be termed "vegetative instability," and the results of the drug tests vary, depending on when the tests are made. If this supposition is true, the cause of this instability still remains to be explained and its relative importance in the production of a seizure properly interpreted.

SUMMARY OF LABORATORY OBSERVATIONS ON SEVENTY-THREE EPILEPTIC PATIENTS

1. Gastric Studies¹

Complete absence of free hydrochloric acid in 11 per cent of the 53 patients studied (nos. 7, 11, 24, 31, 50, 57 and 60).

2. Blood

A. Formed Blood Elements, Interparoxysmal Period (57 patients)

Low platelet count (nos. 16 and 65)	2
Prolonged coagulation time	10
(nos. 2, 5, 19, 20, 21, 28, 49, 52, 61 and 65)	
Increased resistance of erythrocytes (no. 65)	1
Leukocytosis (nos. 22, 46 and 54)	3
Leukopenia (nos. 16, 19, 34, 37, 48, 53, 68 and 70)	8
Lymphocytosis (nos. 1, 6, 17, 20, 27, 28, 32, 39, 44, 49 and 50)	11

B. Formed Blood Elements, Paroxysmal Period (12 patients)

Leukocytosis (nos. 9, 13, 31, 57, 61, 63, 64 and 65)	8
Lymphocytosis (nos. 4, 9, 13, 31, 56, 57, 58, 61, 63, 64 and 65)	11

70. Tinel, J.: Nouvelles conceptions et nouveaux traitements de l'épilepsie, *Médecine* 3:366, 1922.

C. Chemistry, Interparoxysmal Period (55 patients)	
Dextrose	
Hypoglycemia (nos. 9, 10, 13, 28, 44, 45, 49 and 63).....	8
Hyperglycemia (nos. 21, 24, 37, 40, 58 and 65).....	6
Uric Acid: Increase (nos. 2, 5, 21, 24, 25, 34, 36 and 37).....	8
Chlorides: Increase	36
(nos. 3, 4, 6, 8, 9, 10, 11, 12, 17, 20, 21, 24, 25, 26, 28, 29, 31, 32,	
34, 37, 39, 40, 44, 45, 52, 55, 57, 58, 60, 61, 62, 63, 68, 69, 70, 71)	
Of these, 69 (800), 62 (850).	
D. Chemistry, Paroxysmal Period (11 patients)	
Dextrose: Hypoglycemia (nos. 13, 24 and 67).....	3
E. Effect of Salt-Poor Diet on Chemistry (41 patients)	
Dextrose: Hypoglycemia (29, 44, 57, 60).....	4
Uric Acid: Increase (nos. 11, 21, 34, 36, 39, 51, 62, 68, 69 and 71)..	10
Chlorides: General reduction	
F. Wassermann Reaction (73 patients)	
Positive (nos. 16, 41 and 73).....	3
3. Renal Function	
A. Phenolsulphonphthalein excretion (33 patients): Diminished.....	15
(nos. 3, 9, 12, 17, 20, 24, 27, 28, 29, 32, 45, 50, 52, 62 and 63)	
B. The 24 Hour Urine (59 patients)	
Albumin or casts (nos. 3, 7, 12, 13, 17, 32, 33, 54, 57 and 73).....	10
C. Paroxysmal Urine (3 patients)	
Albumin or casts (nos. 8, 10 and 27).....	3
Dextrose (no. 27).....	1
D. Fractional Urine Studies (30 patients)	
Polyuria, nocturnal (nos. 4, 24, 26, 36, 38, 48, 60, 65, 68 and 70)....	10
Fixation of specific gravity (nos. 34, 37, 51 and 54).....	4
E. Effect of Salt-Poor Diet on Urine (54 patients)	
General high chloride excretion lowered during course of diet	
4. Sugar Tolerance (47 patients)	
Glycosuria (nos. 1, 2, 16, 19, 21, 25, 26, 31, 35, 48, 52, 53, 60, 62 and 63)..	15
5. Spinal Fluid (24 patients)	
Positive Wassermann reaction (nos. 5, 16 and 54).....	3
Paretic colloidal gold curve (no. 5).....	1
6. Protein Sensitization (44 patients)	
Food or bacterial	0
Homologous serum (epileptic).....	0
7. The Sputum (61 patients)	
Entirely negative by routine and biologic methods specified	
8. The Feces (60 patients)	
Constipated stools	23
Fluid feces	7
Gross blood (no. 64).....	1
Poorly digested protein (nos. 22, 23, 49, 55, 57, 61 and 62).....	7
More than 30 per cent gas after Schmidt diet (nos. 8 and 27).....	2
9. Cardiac Function and Electrocardiographic Studies (58 patients)	
Bradycardia (nos. 4, 5, 6, 9, 10, 20, 26, 27, 28, 30, 45, 60 and 61).....	13
Mitral stenosis (no. 55).....	1
Mitral insufficiency (nos. 31 and 40).....	2
Bradycardia and sinus arrhythmia (nos. 26 and 69).....	2
Aortic dilatation (no. 18).....	1

Neurocirculatory asthenia (nos. 36, 48 and 68).....	3
Ventricular predominance (nos. 7, 13, 16, 31, 35, 44, 62 and 63).....	8
Extrasystole (nos. 19 and 24).....	2
10. Blood Pressure	
Diurnal variations (29 patients): essentially physiologic	
Postseizure variations (22 patients): increase in blood pressure proportional to the number and severity of the seizures and due to muscular exertion	
11. Basal Metabolic Rate (36 patients)	
High basal metabolic rate (nos. 3, 4, 35, 60, 61 and 62).....	6
Averages well with control group	
12. Roentgenographic Studies	
A. Skull (60 patients) Including Only Well Recognized Abnormalities	
Female type (nos. 11, 13 and 40).....	3
Acromegalic type (nos. 9 and 65).....	2
Brachiocephalic type (no. 12).....	1
Dolichocephalic type (no. 60).....	1
Syphilitic skull (nos. 3, 18 and 58).....	3
Traumatic changes (nos. 5, 7, 13, 16, 20, 43, 57, 61, 67 and 70).....	10
Increased intracranial pressure (nos. 7, 9, 10, 34, 57 and 62).....	6
Calcification of pituitary gland (no. 25).....	1
Pituitary tumor (no. 39).....	1
Irregularity of internal table (nos. 47 and 52).....	2
Irregularity of external table (no. 57).....	1
Brain tumor (no. 62).....	1
B. Thorax (55 patients)	
Active or healed tuberculosis (nos. 13, 17, 27, 45, 48 and 61).....	6
C. Thyroid Gland (35 patients): Enlargement (no. 26).....	1
D. Thymus (35 patients): Persistent (no. 26).....	1
E. Teeth (59 patients): Retained root or periapical abscess.....	30
13. The Sympathetic Nervous System	
Vagotonic types (from 33 to 37 patients).....	18
(nos. 5, 7, 13, 17, 20, 24, 25, 27, 29, 31, 32, 39, 40, 45, 47, 50, 63 and 68)	
Sympatheticotonic types (47 patients)	
(nos. 2, 6, 10, 11, 20, 21, 22, 24, 26, 31, 32, 34, 35, 36, 47, 50, 58, 60, 62, 65, 69 and 71).....	22

CONCLUSION

An intensive laboratory study of seventy-three epileptic patients has been presented and the observations compared with the more limited investigations of other authors. The data reveal significant variations and suggest a more careful study of individual epileptic patients as a clue to the pathogenesis of epilepsy.

BRONCHIAL ASTHMA

THE SEVERE CHRONIC INTRACTABLE TYPE*

I. S. KAHN, M.D.

SAN ANTONIO, TEXAS

It is with considerable temerity that I bring up this subject, probably the most difficult and disheartening in the whole domain of allergy. Still, it is one that all workers in this field occasionally have to face. I am referring to the ill, disabled person with chronic asthma—the chronic daily user of epinephrine, often in heavy dosages and often over a period of several years, with occasional exacerbations requiring the hypodermic administration of morphine, often for several days at a time. Nasopharyngeal operations have been performed, vaccines, pollen extracts and nonspecific therapy of all sorts have been employed, and various changes of residence and dietary measures tried, all to only temporary, partial or no avail.

The patients are usually over 20 years of age, ordinarily poorly nourished and in miserable general condition. Loss of weight is considerable, and hypotension is the rule. Physical examination usually shows no pathologic process other than the persisting asthma with its accompanying bronchitis. Emphysema and changes in the chest wall are usually present. Laboratory tests do not reveal any unusual urinary or blood changes beyond secondary anemia. Eosinophilia, commonly accompanying allergic manifestations, is ordinarily not seen; in fact, in several counts on some of these persons in my practice, no eosinophils have been detected.

In diagnostic skin tests, by the ordinary dermal or intradermal methods, the reactions are usually either negative altogether or negative to the ultimately determined causal factors.

With the vast majority of cases of bronchial asthma at the present time on a demonstrable allergic basis, there seems to me no reason, beyond the previous failure to secure results under ordinary competent allergic management, for a different assumption in these difficult cases. The successful results ultimately secured in a number of these apparently hopeless incurable failures demonstrates the fact that many, if not all, of these cases are specifically allergic and not bacterial or reflex, whatever this term may signify, and that allergic measures carried out over a sufficient period of time will finally give the desired relief in at least a percentage of these instances.

* Submitted for publication, Jan. 7, 1930.

Negative reactions to skin tests, as has been demonstrated, do not bar the possibility of definite pollen or other specific etiology in bronchial asthma and other allergic conditions.

While most cases of seasonal hay-fever, with or without complicating asthma, clear up almost immediately with the cessation of the etiologic pollen season, such immediate recovery is not invariable. Often there is a delay of several days, even in the absence of any apparent coincident infection of the upper respiratory tract. In proved pollen-free rooms and with the use of pollen filters, definite cases of pollen hay-fever and asthma vary in the number of days required to obtain freedom from symptoms. This is also Cohen's¹ experience.

Granting previous approximately identical atmospheric antigen dosages, such differences can only be accounted for either by individual variations in the time required for the production of the necessary quantity of antibody needed for pollen toxin neutralization or by individual variations in the ability to excrete completely such toxin or toxins. Probably both factors are involved.

From a limited investigation of these slowly clearing cases, as stated previously, eosinophilia apparently is relatively not marked or is absent altogether. If one regards the eosinophil as the particular hematologic defensive, as well as the diagnostic, element in allergic conditions, this observation is significant. Not enough work, however, has been reported along this line for one to draw any definite conclusions.

I am advancing the theory that the absence of the expected positive skin reactions in these cases may be due to the failure of resistance, precisely analagous to the absence or disappearance of the previous positive Pirquet reaction in progressive advancing or acute tuberculosis.

The constant, daily, frequently repeated use of epinephrine may be advanced as another factor in the failure to elicit the usual cutaneous response to the causal antigens. But against this is the fact that in patients suffering acutely from hay-fever, the administration of this drug, to secure temporary relief, when followed even at once by the administration of pollen extracts intradermally, as originated by Phillips² for the coseasonal treatment for hay-fever, does not prevent or even delay the usual wheal and erythema reaction. So there is at least a possibility that negative skin reactions are due to a lack of antibody formation as well as a low degree of sensitivity, especially in early cases in young children, as reported last year.³ This does not mean that

1. Cohen, Milton B.: Personal communication to the author.

2. Phillips, E. W.: Relief of Hay Fever by Intradermal Injections of Pollen Extract, *J. A. M. A.* **86**:182 (Jan. 16) 1926.

3. Kahn, I. S., and Grothaus, Emma M.: Incidence and Significance of Negative Skin Tests in Pollen Asthma in Infants and Young Children, *J. Lab. & Clin. Med.* **13**:949 (July) 1928.

frequently repeated daily doses of epinephrine may not account for the failure to elicit the usual cutaneous response in some of these cases.

The following case is typical of the unusual length of time required for the disappearance of symptoms following removal from antigen contact.

REPORT OF CASES

CASE 1.—S. S., a banker, aged 52, who was first seen on Jan. 17, 1926, gave a history of steady and almost constant asthma for six months. Skin tests, given intradermally with 1:50 extracts, yielded slightly positive reactions to the grasses and very questionable ones to the ragweeds; otherwise the results were completely negative. Treatment was declined. The patient entered a hospital in San Antonio on Sept. 17, 1928, in a desperate condition, with a history of daily attacks of asthma for over a year, during which time he had increased his self-administered doses of epinephrine to 12 or 15 minims (0.74 or 0.92 cc.) every two or three hours. His condition became considerably worse with the onset of the ragweed season. Epinephrine was taken at times almost hourly, and occasionally with morphine or codeine, drugs to which he was later demonstrated to be nonsensitive. The onset and subsequent history in this case suggested a pollen etiology. The patient was considered too ill for retesting or for specific treatment. He was placed in a pollen-free room with a filter that was constantly in operation. Epinephrine and morphine were used as indicated, epinephrine being given almost hourly and morphine in one-fourth grain (0.016 Gm.) doses three or four times daily. He was desperately ill, requiring special attention day and night, delirious and on the verge of dying several times in the first forty-eight hours. Improvement started at the end of five days. He remained in the hospital for three weeks, at the end of which time narcotics were discontinued entirely and epinephrine was decreased to six doses daily. He then returned home to a neighboring city, where he remained constantly in bed behind a pollen filter until early in January, 1929. During this period there were two severe relapses, each of several days' duration, requiring an increase of morphine and epinephrine. No other drugs or medication, specific or otherwise, was used. The only break in the pollen-free environment was on the day when he was transported to his home from the hospital. Complete recovery for the first time in two years occurred on Dec. 29, 1928. Up to the present writing (Jan. 26, 1929), he has remained well and has not used epinephrine.

The interest in this case lies in the fact that in a ragweed-free room, as demonstrated by frequent pollen plates, complete freedom from symptoms did not occur until three and a half months after removal from all possible ragweed contact, or, if one considers the pollen filter as only partially efficacious, in spite of the failure of pollen plates to detect ragweed pollen, not until at least one and a half months after the last possible atmospheric contact with ragweed. It will be noted that the ragweed tests performed even two years previously gave practically negative results. I regret that no examinations of the blood were made in this case.

The permanent loss of a known original, definite, strong, positive skin reaction during the course of protracted severe asthma is a more conclusive proof of this conception of practically complete failure of allergy

antibody formation or its early exhaustion, and is illustrated by the following case:

CASE 2.—I W. B., a physician, aged 37, was first seen on July 2, 1928. The first attack of hay-fever occurred in May, 1927, in Mississippi. At this time he was tested by the dermal method. He gave huge positive reactions to grasses and ragweeds. His arm swelled badly and the hay-fever markedly increased. The first attack of asthma occurred in October, 1927, since which time (eighteen months) there had not been a single day of freedom and not a single night of unbroken sleep. From the start, epinephrine was required at least every three hours and frequently every hour. He was intolerant to morphine and its derivatives. The seasonable onset of his hay-fever and later his asthma obviously corroborated the pollen etiologic diagnosis. One month after the onset of the asthma the patient was tested by another allergist (Dr. Balyeat, of Oklahoma City)⁴ and found to give positive reactions to house dust and feathers. The reactions to the pollen tests were so reduced in size only six months after the first attack of hay-fever as to be recorded as inconclusive or only slightly positive.

When he was first seen, this patient's condition was pitiable to an extreme degree. He was 72 inches (182.8 cm.) tall and weighed 109 pounds (49.4 Kg.), having lost 40 or 50 pounds (18 or 22 Kg.). His hair had turned completely gray, giving him an appearance at least twenty years older than his actual age. He could scarcely walk or stand. Pallor was marked, and the entire picture was that of advanced tuberculosis or carcinomatosis. However, the most searching repeated examinations, clinical, roentgenologic and laboratory, by myself and consulting internists, revealed nothing beyond a mild secondary anemia. Not a single eosinophil was encountered in a number of blood smears. Whether a previous extensive intra-nasal operation had anything to do with the loss of resistance in this case is, of course, purely conjectural. There was some intermittent nasal suppuration, not marked. The nasal mucosa, however, remained almost constantly in an uncontrollable state of typical allergic hypersensitiveness, with profuse watery discharge. This yielded slightly, and only temporarily, to ephedrine or cocaine derivatives. The paroxysms of asthma were severe and unbroken, except when the patient was under the influence of epinephrine.

The patient was placed in a pollen-free room, both home-made and commercial filters being made. Frequent plates showed this room free from pollen, fiber and dust, except on one or two occasions. The patient was a highly intelligent physician, who was thoroughly conversant with the literature on bronchial asthma and keenly on the lookout for nonspecific and specific antigens. All known antigenic foods were in turn removed from his diet, all to no avail. Though several periods of improvement and relapse followed, as is the rule in these cases, epinephrine was never reduced below three doses in twenty-four hours, even after a six months' sojourn in this environment. He was considered too ill for any considerable amount of testing. However, in November, dermal tests with both grasses and ragweeds gave absolutely negative results. Several recognized accidental introductions of ragweed pollen in his room, as proved by plates, were invariably followed by severe relapses which lasted a number of days. A thermometer was installed so as to permit the detection and correction of any wide variations in temperature. Feathers, animal hair, wool and odors were completely eliminated.

After six months of this routine, he recovered enough strength to be up for several hours daily, and real improvement seemed at last well on the way. Epinephrine

4. Balyeat, R. M.: Personal communication to the author.

was almost dispensed with. As the ragweed season had been over for a month, he was permitted to stop the operation of his filter to maintain more warmth. All went well for about ten days, when about December 25 with the onset of the winter mountain cedar pollination, a severe relapse ensued. It was then noticed that the patient in the adjoining room had had one of these pollinating trees installed as a Christmas decoration. Pollen plates in my patient's room were loaded with this pollen. He was then advised to leave San Antonio to go to Memphis, where at that time there was no atmospheric pollen. He was instructed to continue antigenic precautions. During the winter months there, epinephrine was reduced to four or five doses daily, with considerable improvement in his general condition. With the onset of the tree pollination season in Memphis, he relapsed again into his former state. Having no filter at that time, he was ordered to a densely settled portion of Chicago. Slow improvement again set in. However, in April, without advice, he took several 1:250,000 dilution doses of timothy pollen extract. This was followed by a decided relapse, which lasted until the present writing (May 27). When last observed, pollen plates showed his room to be pollen-free.

This case seems to me to represent an extreme degree of lack of antibody formation against pollen toxemia, combined with extreme pollen hypersensitiveness. In the light of present knowledge, specific or nonspecific therapeusis in my judgment was too risky to attempt. In my opinion, his only chance, as in all cases of this type lies in the hope that prolonged strict removal from antigen contact will ultimately lead to some natural restoration of the antipollen defensive mechanism, and render possible the subsequent exhibition of the usual specific methods of desensitization.⁵

It is conceded that I am unable by laboratory methods to advance any scientific proof either of this point of lack of antibody formation or of the inability to excrete allergic toxins, or for that matter, even of correct etiologic diagnosis. This article is merely the presentation of suggestive clinical cases. In not a single case of this series have I been able to secure positive reactions by the intradermal injection of undiluted blood serums into persons known to be very sensitive. In a similar manner, none has shown positive reactions by the passive transfer method.

To note the possibility of delayed excretion from the bronchial mucosa, a number of centrifugated sputum examinations were made following the close of the presumed etiologic pollen season, but the only pollen granules identified were those of the current pollen season. This, of course, does not preclude the possibility of alteration in pollen morphology by prolonged contact with bronchial mucus, making microscopic identification impossible.

5. As a further corroboration of this idea, as a result of the persistent continuance of antipollen precautions, by March, 1930, this patient was able to resume medical practice; eosinophilia (from 6 to 15 per cent) returned during rare light attacks, the original pollen skin tests were positive, and the patient was able to tolerate specific pollen treatment in comparatively high dosages.

The third possibility in connection with these cases, apparently borne out by repeated clinical observation, is that the failure to develop antibodies to their original antigenic factor renders them highly sensitive and nonresistant to numerous other known antigenic factors of no biologic relationship to the original excitant. In other words, other pollens, wool, feathers, cold air, foods and inhalant irritants can prolong the asthmatic state indefinitely for months or even years following the cessation of the pollination season in an original ragweed case, and often when no complicating infectious process is detectable. Frequently, patients who are not severely ill with asthma of ragweed etiology sooner or later develop sensitiveness, both cutaneous and clinical, to other pollens and also to these other antigens.

A word of warning should be mentioned regarding the use of the usual diagnostic skin tests in the cases of severe prolonged asthma. Immediate testing should not be done. Not only do such tests reveal negative reactions to later determined causal antigens, especially if pollen is a prime factor, but the futility of such testing seems complicated by the fact that there is frequently a high degree of systemic absorption from their employment. This was learned from bitter experience, when it was my custom to make a routine, thorough and complete test in every case of asthma. It was noted that a number of patients who showed immediate improvement in a pollen-free or completely antigen-free environment, giving every promise of total disappearance of symptoms within a few days, had relapses after such testing, especially with the pollens; the relapses were of marked severity, bordering in a few instances on a fatal outcome, and at times lasting for weeks. The conditions were such that only the tests could be incriminated. As an allergy worker, it was only with the greatest reluctance that I came to this conclusion. These untoward results have occurred especially when, after negative dermal reactions, negative reactions to 1:5,000 and 1:500 extracts used intradermally were followed by the use of 1:50 material. However, I have seen such relapses follow even the dermal tests or intradermal tests with 1:5,000 extracts.

Pollen tests, even by the intradermal method, can be made later with more safety, and few relapses, when the case has either cleared up completely or been kept under control by minimal dosages of epinephrine, provided such tests are made singly, infrequently and with carefully graduated extract strengths, when no setback from each previous dosage is noted. Even under such circumstances, positive reactions to skin tests are rarely securable, unless one considers diagnostically specific the constitutional relapse that occurs within twenty-four or forty-eight hours after the use of a pollen extract, intradermally or hypodermatically. These relapses often do not begin immediately after testing, the inception not occurring until twenty-four, forty-eight or seventy-two

hours later. Following the onset of the relapse, there is a steady increase in the severity of the symptoms for several days before a climax is reached. This climax is then maintained at times for weeks, clearing up only by a slow lysis which may cover another period of weeks.

If one is blocked by contraindicated diagnostic skin tests, how then is it possible to arrive at the etiologic factor or factors of these cases? A lengthy history is of immense value. Details are sought regarding the date and circumstances of the initial attack, the preceding bronchitis or hay-fever, seasonal exacerbations, the response in the form of improvement or relapses in various localities or places of residence, especially if seasonal, the effects of weather, winds, and drafts, sleeping indoors and outdoors, the effects of various kinds of pillows and known or suspected fiber, hair, dust and odor contact, aversion to various foods and drugs, and the presence or absence of urticarial or eczematous cutaneous manifestations.

Given a good working knowledge of the botany of hay-fever and of usual and unusual allergic antigenic factors, ordinarily without proceeding further a decidedly reasonable and not infrequently accurate presumptive etiologic diagnosis can be made, subsequently confirmed by environmental tests in the absence of securable laboratory confirmation. Even when its presence, previous or concurrent, is absolutely denied, it is remarkable in how many of these cases competent examination will show mild but definite typical allergic vasomotor rhinitis, frequently without other nasal disease; if such disease is present, it seems to be without any clinical bearing.

It is inconceivable to me that a nonresistant case of this type can remain one of single antigenic etiology. Also, it is immaterial whether animal hair or pollen was the initial originating excitant. These patients, as seen by the allergy worker, are practically invariably sensitive to both, also to dusts of all kinds, odors, drugs, even at times to morphine, but curiously enough, in my experience, seldom to foods.

On this assumption, these patients are placed behind pollen filters or in hotel rooms on a closed court; feathers, wool and all animal hair contacts are eliminated, rugs covered or removed, and every possible inhalant irritant eliminated. In other words, the environment is made dust, pollen and odor free, and meticulously kept so. Known antigenic foods, such as nuts, onion, honey, milk, eggs, wheat and cereals, are barred. All drugs, except epinephrine or ephedrine, are forbidden. This routine is maintained for weeks or even months if necessary, until recovery occurs, when subsequent specific desensitization can be carried out as indicated. Such specific desensitization should not be used until marked improvement, or preferably complete recovery, has been secured. Ordinarily I do not start such specific treatment until the case is at least down to two or three doses of epinephrine daily. I then begin

with extracts of 1:100,000 or even 1:500,000 dilution, repeated at first at weekly intervals, increasing very slowly and stopping at once with any temporary increase of symptoms. Ordinarily the symptoms of overdosage occur before the incidence of local reactions on the arm; in fact, even small erythematous local reactions are accompanied by severe prolonged relapses.

In presenting this subject, cases of asthma that clear up in this antigen-free environment within seven to ten days have not been considered. This discussion is limited to those cases that do not clear up or in which appreciable improvement is not secured under such conditions in this or even a much longer period of time. The possibility of overlooked or unrecognized antigens in an unknown percentage of these cases is readily admitted. Naturally, the more experienced and observant the allergy worker, the smaller is the number of cases that will fall into this category. Antigen overdosage from tests or specific overtreatment will account for some failures. Omission of called for treatment, specific or nonspecific, will account for others.

If, however, these patients can be persuaded to continue an indefinitely prolonged length of time under antigen-free conditions, freedom from symptoms in a certain admittedly relatively small percentage does occur. However, in several instances, I have seen from six to nine months of this routine required, with many interim severe protracted relapses of no demonstrable etiology.

I offer no apologies for a lack of statistics or for the admission of successful results in only a comparatively small percentage of these instances. Many of these patients drift away, owing either to lack of funds or to disappointment at not securing more prompt relief. Many instances of failure in allergic antibody formation are to be expected until knowledge of the mechanism required for its restitution is attained. Many patients die, after a few years of suffering, from exhaustion, cardiorenal disease or other complications.

To me it seems remarkable that any results can be secured in this type of case. The one ray of encouragement is that the relief secured in an estimated 10 per cent of my cases shows that by adhering to standard allergic methods of management, I am at least on the right track in handling all my cases of bronchial asthma no matter how stubborn or severe, and that the entity of intrinsic nonallergic asthma, as these cases would ordinarily be classified, is probably nonexistent.

The most discouraging feature of the type of cases I am describing is the extent of time, many weeks and even months, required to secure relief from symptoms, and the distressing number of frequently inexplicable explosive severe relapses before this relief is ultimately secured.

A somewhat similar state of relapse is seen in tuberculosis. It not infrequently happens that under strict rest in bed, the afternoon temperatures will gradually fall to normal. In spite of the strictest rest and even in the absence of complications, after a few days of such normal temperature there occurs a second rise of afternoon temperature lasting days or weeks and falling by slow lysis. Even a third or fourth repetition of this process will at times happen before a basic normal afternoon temperature is attained.

This long extent of time required for the clearing up of these cases of asthma, however, seems to me rather conclusive proof of the existence of a type of asthmatic subject who lacks ordinary resistance to allergic antigens, or who shows a markedly diminished ability to excrete their toxins.

CONCLUSIONS

1. There exists a type of asthmatic person in whom, even in the absence of other complications, antibody formation against allergic antigens or the allergen resistance factor, whatever that may be, is apparently greatly reduced or nonexistent, precisely as is the case analogously in tuberculosis and other bacterial infections.

2. In the absence of antigen reproduction, such as occurs in bacterial infections, there is probably combined with this lowered faculty of antibody formation a definite inability to excrete promptly the toxins elaborated by such allergic antigens following their complete withdrawal.

3. Eosinophilia is usually absent in these cases.

4. The usual diagnostic skin tests cause negative reactions, and if pollens are used, are dangerous.

5. In these cases there is gradual, and at times rapid, development of polyantigenic sensitiveness of high degree.

6. A small but appreciable percentage of these patients recover a certain amount of antibody formation and relief and even freedom from symptoms after many weeks or months of persistent elimination of antigenic contact without the institution of other therapeutic measures.

7. While there is no laboratory proof to support these contentions, the clinical results secured offer rather conclusive proof.

8. There exists no known reason why a patient should not fail to develop antibodies to allergic as well as to bacterial antigens.

ARTERIAL HYPERTENSION

EVALUATION OF THE PROGNOSIS *

EDWARD J. STIEGLITZ, M.D.

CHICAGO

A marked increase in the average mortality over the expected norm occurs in persons with arterial hypertension.¹ Great variations occur, however, and it is not without difficulty that the question of individual prognosis can be answered. The patient's inevitable query, "Will I get well? Can my blood pressure be reduced?" warrants careful attention. Large masses of statistics reveal merely the mean or average data, and all individual variations are ironed out. The patient is naturally not particularly interested in the average outlook for the group, but is vitally concerned in his own personal problem. The height of the arterial tension is wholly inadequate as a sole criterion of the prognosis;² the degree of diastolic hypertonia represents merely one of several factors which must be given due consideration.

Among the important factors affecting the prognosis in any specific clinical instance are: the age of the patient; the duration of the vascular disease; the etiologic factors involved; the degree of permanent, irreparable arteriolar sclerosis which has occurred; the association with other complicating disturbances such as cardiac or renal injury, diabetes or pregnancy, as well as the height of the diastolic arterial tension. As age increases, the life expectancy of course declines synchronously, but increasing age is not of great significance in altering the prognosis in hypertension. The average therapeutic response in patients from 60 to 70 years is as good as or better than that of younger patients.³ The duration of the vascular disease is, however, a prominent factor in prognosis. The longer the duration of hyperpiesis, the greater the degree of arteriolar muscular exhaustion and replacement fibrosis or arteriolar sclerosis. Extensive arteriolar sclerosis being the end-point of the slow pathogenic progression, and being clearly an irreversible process, is of poor prognostic import. The arterial vessels may to some degree reveal the extent of such irreparable arterial changes,⁴ but in certain

* Submitted for publication, Jan. 31, 1930.

1. Fahr, G.: *Am. J. M. Sc.* **175**:453 (April) 1928.

2. Post, W. E., and Stieglitz, E. J.: *Am. J. M. Sc.* **171**:648 (May) 1926.

3. Stieglitz, E. J.: *Arterial Hypertension*, Chapter VI. In press. New York, Paul B. Hoeber, Inc., 1930.

4. Agatston, S. A.: *Fundus as Definite Index to Arterial Diseases with Analysis of 100 Cases*, *Arch. Int. Med.* **42**:455 (Oct.) 1928.

instances this information may be misleading, as these vascular degenerative changes do not proceed at the same pace throughout the body.⁵

The significance of the etiologic background lies in the varying degree to which various factors are amenable to therapy. If hereditary predisposition to premature vascular degeneration is conspicuously manifest in the family history, it is of course of no avail to hope for any change in the intrinsic constitutional physiologic make-up of the individual patient. The influence of such heredity on vascular disease is irrevocable.⁶ On the other hand, should specific infections such as dental sepsis or syphilis be regarded as significant, therapy may be expected to accomplish much. The same encouraging attitude may be taken with other etiologic factors such as dietary indiscretions, thyrotoxicosis and metallic poisoning. Typhoid fever in the past histories of patients with hypertension apparently affects the prognosis adversely.⁷

When extensive renal injury is found associated with arterial hypertension, the prognosis is definitely darker.⁸ In part the greater hazard arises from the nephritis per se, in part from the anemia usually associated with chronic renal disease. The presence or absence of albumin or casts in the urine is not a sufficient criterion of renal injury, nor is the degree of albuminuria any index to the severity of the renal lesion. Severe renal failure may occur with no appreciable quantity of albumin in the urine. Severe renal disease occurs in only a small percentage of cases of hyperpiesis,⁹ although mild renal injury is common. Of fundamental importance for proper recognition of the severity of the renal injury are functional studies, either with phenolsulphonphthalein, urea concentration, the Mosenthal test or more simply and with greater effectiveness with the concentration test.¹⁰

The greatest menace to life in hypertensive arterial disease is cardiac defeat or exhaustion.¹ It is important, therefore, to evaluate the status of the cardiac reserve. Estimation of the surplus of cardiac energy

5. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, *Arch. Int. Med.* **35**:650 (May) 1925; Arterial Lesions of Glomerulonephritis, *ibid.* **40**:80 (July) 1927.

6. Barach, J. H.: Constitutional Factors in Hypertensive Diseases, *J. A. M. A.* **91**:1511 (Nov. 17) 1928. Draper, G.; Allen, G., and Spock, J. C.: Studies in Human Constitution; Clinical Genetics, *ibid.* **92**:2149 (June 29) 1929.

7. Kalt, M.: *Bull. Soc. d'ophth.* **6**:309, 1928; Thayer: *Bull. Johns Hopkins Hosp.* **15**:313, 1904.

8. Addis, T.: Clinical Classification of Bright's Disease, *J. A. M. A.* **85**:163 (July 18) 1925.

9. Paullin, J. E.; Bowcock, H. M., and Wood, R. H.: *Am. Heart J.* **2**:613 (Aug.) 1927.

10. Fishberg, A. M.: Unitary Nature of Impairment of Renal Function, *Arch. Int. Med.* **38**:259 (Aug.) 1926.

is not easy by specific tests.¹¹ Electrocardiographic studies of the heart in hypertension do not give particularly useful information unless an extensive myocardial degeneration has taken place, and they are then unnecessary.¹² Left ventricular preponderance is usually, although not invariably, present.¹³ Organic valvular disease of the heart affects the prognosis adversely.¹⁴ The most significant early signs of myocardial weakness are undue dyspnea, undue tachycardia and cardiac consciousness or precordial distress occurring on exertion. The occurrence of these is best revealed by the patient's history.¹⁵ Such signs of myocardial weakness make for a bad prognosis.¹⁶

Consideration of the factors mentioned which affect the prognosis in arterial hypertension emphasizes the complexity of the problem. However, the most important factor in the evaluation of the prognosis is the extent of permanent vascular injury. Hypertensive arterial disease is a slowly progressive process,¹⁷ starting with increased arteriolar tonicity, with gradually appearing medial muscular hypertrophy,¹⁸ and later, fatigue as the process continues. The muscular fatigue leads to increased muscular irritability, further spasticity and more fatigue. Thus a vicious circle is introduced which tends to perpetuate the process, although the original initiating irritating factors may have ceased to exist.¹⁹ With further fatigue exhaustion occurs, and degeneration of the muscle fibers, with their gradual replacement by fibrous connective tissue, or arteriolar sclerosis appears. This fibrosis is not an invasive process, but a protective one to replace the exhausted and dead muscle cells. At this point the process becomes irreversible; prior to this stage, when the hypertension is due to muscular hypertonia, the process is relaxable, reversible and amenable to therapy. The pathogenic development from transient arteriolar spasticity to permanent collagenic scarring of the arteriolar walls is a slow, gradual, but

11. Baráth, E.: *Ztschr. f. d. ges. exper. Med.* **54**:58, 1927. Wallace, J. H.: Stair Climbing as a Test of Cardiac Function, *Am. J. Dis. Child.* **28**:282 (Sept.) 1924.

12. Ziskin, T.: Electrocardiogram in Hypertension, *Arch. Int. Med.* **42**:512 (Oct.) 1928.

13. Allan, G. A.: *Heart* **12**:181, 1926.

14. Cowan, J., and Fleming, G. B.: *Quart. J. Med.* **5**:309, 1912. Pitt, J. N.: *Brit. M. J.* **2**:118, 1887. Goodhart, J. J.: *Lancet* **1**:479, 1880.

15. MacKenzie, Sir James: *Diseases of the Heart*, ed. 4, Oxford, Oxford Med. Publications, 1925, p. 17.

16. Herrick, W. W.: *Ann. Int. Med.* **3**:467 (Nov.) 1929.

17. Stieglitz, E. J.: *Arterial Hypertension*, Chapter II, in press, New York, Paul B. Hoeber, Inc., 1930.

18. Hernohan, J. W.; Anderson, E. W., and Keith, N. M.: Arterioles in Cases of Hypertension, *Arch. Int. Med.* **44**:395 (Sept.) 1929.

19. Stieglitz, E. J.: *J. Pharmacol. & Exper. Therap.* **32**:23, 1927; **34**:407 (Dec.) 1928.

persistent evolution. The patient may be seen at any stage. Therefore to prognosticate properly it is of the utmost importance to determine the phase of development.

There are several criteria on which such identification may be based. The duration of the hypertension is an important factor. But the duration is unknown in the majority of instances, as hypertension is most asymptomatic in its early course and is frequently discovered accidentally. Persistence of diastolic hypertension is significant. If the diastolic pressure is maintained at 135 mm. or higher, the outlook for the patient is very dubious,²⁰ and renal impairment is to be expected.²¹ Persistent diastolic hypertension is more significant than transient excessive hyperpiesis, as the degree of variability in the height of the diastolic tension constitutes an indirect but effective criterion of the extent of irrevocable arteriolar changes. In the presence of marked arteriolar sclerosis the peripheral resistance, as measured by the diastolic pressure, cannot vary greatly; it is relatively rigid or fixed, whereas with the purely functional spasticity of early vascular disease the arterial tension is characteristically fluctuant and variable. To determine whether the diastolic tension is or is not variable requires time and repeated observations, and the patient's justified demand is for a relatively immediate answer.

This information may be obtained in a very simple way. The soluble nitrites cause rapid and marked relaxation of the arterial tone and a corresponding fall in the blood pressure.²² It has been pointed out¹⁹ that as this vasodilator effect is so fleeting and transient, the soluble nitrites are of relatively little use in the therapy of arterial hypertension. For the purpose of observing the degree of relaxability of the arterial system, however, the soluble nitrites are invaluable. Amyl nitrite has proved most satisfactory because of its prompt efficiency in causing vascular relaxation, because it is so readily administered by inhalation from pearls and because the action is very brief. It is also useful as a gastro-intestinal antispasmodic²³ and in acute cerebral vasoconstriction.²⁴ Its effect on the pulmonary arteries is the same, though less marked, as on the systemic vessels.²⁵ The vascular dilation and

20. Lian, C.; Broca, R., and Clément, J.: *Presse méd.* **29**:743, 1921.

21. Stieglitz, E. J.: *Illinois M. J.* **50**:234 (Sept.) 1926. Hamman, L.: *W. Virginia M. J.* **24**:157 (April) 1928.

22. Clendening, L.: *Drugs, Modern Methods of Treatment*, St. Louis, C. V. Mosby Company, Chap. II, 1924. *Sajous: Analytic Cyclopedia of Practical Medicine*, Philadelphia, F. A. Davis Company, 1915, p. 48.

23. Holmes and Dresser: *Am. J. Roentgenol.* **19**:44, 1928.

24. Frevez: *Bull. et mém. Soc. nat. de chiv.* **54**:238 (Feb.) 1928.

25. Love, G. R.; McGuigan, H., and Wiley, C. E.: *J. Lab. & Clin. Med.* **10**:885 (Aug.) 1925.

reduction of the blood pressure does not occur or is very slight in patients with extensive arteriolar sclerosis.²⁶

The test is carried out as follows: After determination of the arterial tension, a pearl containing 5 minims (0.3 cc.) of amyl nitrite is broken, and the patient is asked to inhale deeply three or four times with the liquid held directly under the nose. As this is done, or immediately thereafter, the patient becomes very flushed and may perspire freely and complain of a sense of vertigo or impending syncope. It is at this time that the arterial tension is again determined, as at this moment the tension is at its lowest, the symptomatology being attributable to the acute vasorelaxation. During the period of flushing there is usually a tachycardia, sometimes, although not invariably, accompanied by cardiac consciousness or palpitation. The second observation of the blood pressure, at the minimum level, should be checked several times in rapid succession. After this the discomfort of the acute relative hypotension may be abbreviated by the administration of aromatic spirits of ammonia, either orally or by inhalation.

The response to this test in patients with arterial hypertension varies greatly. The degree with which the diastolic pressure approaches the normal level may be taken as a prognostic criterion of considerable moment, and also serves as an objective in therapy. The diastolic tension may fall below normal levels in early, purely spastic instances of hypertension, whereas in late cases with extensive fibrotic arteriolar changes, the fall may be relatively slight and it may be concluded that no therapeutic management can yield good results.

The accompanying tabulation of the results obtained with this procedure illustrates the type of response encountered, the interpretation given at the time and the therapeutic results obtained several months later. It is notable that in the forty cases cited, the prognostic interpretation was in gross error of the actual therapeutic results in only one instance (case AN 21). As with most clinical tests, the value depends to a great degree on the skill of interpretation. The table also illustrates the fact that age is unimportant as a criterion of the type of response to be expected. It is also manifest that the poorest type of response occurred in patients with reduced renal functional reserve. The author has found this procedure of great assistance in clinical practice. It is by no means finely accurate, nor does it pretend to give extensively detailed information. It has prognostic but no therapeutic use, and is purely a test to determine indirectly but physiologically the relaxability of the arterial system as a whole and thereby to evaluate approximately the extent of anatomic arteriolar damage. The same information is obtained by prolonged clinical observation, but the patient often justifiably demands a more immediate answer to his query.

26. Schert, D.: *Wien. klin. Wchnschr.* 40:113 (Jan. 27) 1927.

The value and usefulness of this test may be further illustrated by a few more detailed specific case examples.

REPORT OF CASES

CASE AN 1.—*History*.—Mrs. R., 60 years old, a widow with one child was first seen on June 19, 1928, at which time an arterial tension of 210 systolic and 120 diastolic was observed. There was a strong hereditary factor in the etiology, as evidenced by four instances of apoplexy in the patient's family. The cardiac

Types of Response, Interpretation and Therapeutic Results of Procedure

AN No.	Sex*	Age	Vascular Tension Before Test	Vascular Tension After Amyl Nitrite	Percent- age of Dias- tolic Return to Normal	Esti- mated Degree of Sclerosis	Prognosis Given at the Time	Time in Mo.	Vascular Tension Later (Results)	Comment
1	♀	60	210/120	130/ 80	100	0	Good	16	145/ 90	
2	♀	55	210/125	152/108	50	+	Fair	16	175/ 90	
3	♀	65	220/140	160/122	40	+++	Poor	2	Died of cerebral hemorrhage
4	♀	57	220/116	122/ 70	100	0	Good	10	158/100	Died of gastric carcinoma
5	♀	57	180/114	140/ 95	60	+	Fair	12	160/110	Mild gout; low renal reserve
6	♀	59	215/145	160/120	30	+++	Poor	8	175/118	
7	♀	55	200/130	170/100	75	+	Fair	9	161/108	Syphilis
8	♀	60	223/108	170/108	0	++	Fair	5	176/106	
9	♀	67	198/110	142/110	0	+++	Poor	5	220/120	Low renal reserve
10	♀	64	178/112	153/102	50	++	Fair	24	160/ 90	Chronic arthritis
11	♀	72	210/ 90	110/ 50	100	0	Fair	16	180/ 80	Thyrototoxicosis with thyroidectomy (basal metabolic rate, 54)
13	♀	54	200/100	160/ 70	100	0	Good	14	150/ 90	Diabetes, myocarditis
14	♀	49	196/140	140/110	70	++	Poor	8	180/120	
15	♂	61	230/130	190/105	50	++	Poor	2	216/ 98	Low renal reserve; died of apoplexy
16	♀	36	160/102	134/ 84	100	0	Good	3	112/ 74	
17	♀	62	180/105	135/100	50	+	Fair	8	166/ 96	
18	♂	36	172/130	130/ 80	100	0	Good	8	144/ 90	Cervical rib with pressure
19	♀	48	190/130	130/105	50	++	Poor	10	190/105	
20	♀	48	180/115	140/ 95	80	+	Fair	8	150/ 96	
21	♀	65	184/106	148/100	40	++	Fair	7	210/110	Wrong prognosis
22	♀	50	200/110	170/105	20	++	Poor	2	190/110	
26	♀	39	180/110	128/ 78	100	0	Good	8	130/ 83	Past thyrotoxicosis
27	♀	36	220/140	170/120	40	++	Poor	3	215/145	Nephritis and anemia
28	♀	55	190/120	170/ 85	100	0	Good	4	152/ 98	
29	♀	49	230/120	170/120	0	+++	Poor	5	210/112	Died of cardiac failure
30	♀	52	240/140	150/100	80	+	Fair	4	196/110	
31	♀	35	180/132	130/ 76	100	0	Good	4	150/ 92	
33	♂	35	170/120	90/ 66	100	0	Good	6	118/ 72	Hypertension for 3 years
34	♀	74	230/100	180/ 95	50	+++	Poor	4	190/100	
35	♀	51	210/140	170/110	70	++	Poor	3	178/110	
36	♀	71	190/115	160/110	20	+++	Poor	13	180/110	Obesity
39	♀	29	190/118	140/100	65	++	Fair	11	175/110	Low renal reserve
40	♀	54	240/150	160/100	90	+	Good	3	155/ 90	
41	♀	39	206/123	164/118	35	+++	Poor	5	220/140	
42	♀	61	202/130	170/ 95	85	+	Fair	3	180/100	
43	♀	36	220/150	180/130	33	+++	Poor	25	240/160	Low renal reserve
44	♀	45	220/130	170/115	40	++	Poor	24	206/110	
45	♀	54	180/140	128/ 84	100	0	Good	3	140/ 80	
46	♂	56	152/105	110/ 78	100	0	Good	9	128/ 74	Cholecystitis with cholecystectomy
47	♀	46	160/103	130/ 88	100	0	Good	12	134/ 90	
48	♀	35	188/110	130/ 80	100	0	Good	8	126/ 75	Past eclampsia and severe nephritis
49	♀	59	245/120	215/120	0	+++	Poor	3	220/130	Retinitis, oral sepsis

* ♂ indicates male; ♀, female.

reserve was poor, with much dyspnea. Pregnancy had occurred when she was 40 years old, with marked intoxication. The renal reserve was reduced, the maximum specific gravity of the urine being but 1.018 after fourteen hours' deprivation of fluids.¹⁰ On inhalation of amyl nitrite, the arterial tension fell to 130 systolic and 80 diastolic.

This marked fall in the diastolic pressure to a normal level indicated an absence of arterial muscular degeneration, and a good prognosis was offered despite the adverse factors of reduced cardiac and renal reserves. This interpretation given at the time was justified by the later course of events. On Dec. 21, 1929, eighteen months later, the arterial tension was 145 systolic and 90 diastolic, and the patient felt well. Therapy had been carried on with bismuth subnitrate.¹⁹

CASE AN 11.—*History*.—Mrs. S. F., aged 73, was first seen on Dec. 9, 1928, at which time the arterial tension was 210 systolic and 105 diastolic. Senility was manifest, with great emaciation and much fear. A coarse tremor was notable. Inhalation of amyl nitrite reduced the arterial tension at once to 110 systolic and 50 diastolic, a tremendous fall. Other than a distressing tachycardia, this violent reaction had no sequelae. Because of the emaciation, the tremor and relatively low diastolic tension, the basal metabolism was determined and found to be plus 54. In August, 1929, thyroidectomy was done after preparation with compound solution of iodine. In January, 1930, the last observations revealed an arterial tension of 170 systolic and 80 diastolic, a 25 pound (11.3 Kg.) gain in weight, and remarkable gain in vigor, considering the advanced age of the patient.

This instance illustrates that age alone is not an adequate criterion anent the amenability of arterial hypertension to treatment, and also that etiologic factors that may be removed, as thyrotoxicosis, affect the prognosis favorably.

CASE AN 15.—*History*.—P. G., a Greek, aged 61, was seen at the vascular disease clinic of Rush Medical College on March 3, 1929. He revealed a blood pressure of 255 systolic and 135 diastolic and a markedly reduced renal reserve. The maximum specific gravity of his urine reached only 1.016 on deprivation of water. On March 6, the amyl nitrite test was carried out. The arterial tension was 230 systolic and 130 diastolic before the test and fell to 190 systolic and 110 diastolic. Because of these data, a poor prognosis was offered. His arterial tension remained high, the lowest observed being 174 systolic and 112 diastolic on April 6. The patient died on May 30 following an apoplectic stroke.

CASE AN 33.—*History*.—J. E. V., aged 36, an industrial chemist, was first seen on Sept. 9, 1929. He stated that for three years he had known that he had hypertension, but that he was not certain concerning the blood pressure prior to that time. The arterial tension was 170 systolic and 120 diastolic. The basal metabolic rate was plus 10. An impairment of the renal reserve was moderate, the maximum specific gravity of the urine being 1.018 after deprivation of fluids¹⁰ and the phenolsulphonphthalein secretion, 50 per cent in three hours. There was no anemia. On inhalation of amyl nitrite, the arterial tension fell from 170 systolic and 120 diastolic to 90 systolic and 60 diastolic. A question arose anent the reason for the reduced renal reserve: whether this was due to renal disease dating from a severe scarlet fever in childhood and aggravated by his daily exposure to fuming phenol, or whether the renal inefficiency was due to circulatory inadequacy because of the arteriolar spasticity. That the hypertension was due solely to spasticity was evident from the excellent vasorelaxation obtained with amyl nitrite. Therefore, a good prognosis was given.

On October 19, the arterial tension had fallen to 135 systolic and 88 diastolic and on October 21 to 140 systolic and 80 diastolic after treatment with bismuth subnitrite. On Jan. 14, 1930, the arterial tension was 118 systolic and 72 diastolic,

and the concentration test of the renal function revealed a satisfactory maximum specific gravity of 1.028. No bismuth subnitrate had been taken since Dec. 21, 1929. The improvement in renal function and the return to normal of the arterial tension confirmed the first prognostic impression, although at first glance and without the amyl nitrite test, the high diastolic tension and evident renal impairment suggested a poor prognosis.

The foregoing case histories serve to illustrate the usefulness of this procedure in evaluating the prognosis in arterial hypertension. In two of the instances cited (cases AN 11 and AN 33) the age of the patient, the high diastolic tension and evidence of renal impairment indicated extensive irrevocable damage, but the relaxability of the arterioles clearly demonstrated that the arteriolar hypertonia had not yet progressed to sclerotic degeneration, and that much could be expected from proper therapy.¹⁹ Consideration of the physiologic mechanism of the peripheral circulation demonstrates that the logic of such a test procedure is sound.

No ill effects attributable to the inhalation of amyl nitrite in hypertension have been observed. The most marked sudden fall in arterial tension occurred in case AN 11, reported in detail. Nor is it felt that ill effects are at all likely to occur. The frequency with which amyl nitrite or nitroglycerol are administered with impunity in angina pectoris indicates strongly that the risk is minor if it exists at all. Therapeutically this procedure is valueless, as the vasorelaxation is far too transient to be of benefit; as an aid in evaluating the prognosis, however, it is most useful. Gradual, persistent and effective vascular relaxation is obtained with bismuth subnitrate.¹⁹

SUMMARY

The prognosis in individual instances of arterial hypertension should be based on several variable factors and does not necessarily coincide with the statistical average prognosis for groups of hypertensive persons. The factor of age is not of great moment. The factor of the etiologic background accounting for the hypertension is significant. Likewise are the status of the cardiac and of the renal reserve of importance. Most significant of all is the stage at which the vascular disease is encountered; whether the hypertension is of purely spastic origin or whether slight, moderate or extensive fibrotic changes have already taken place in the vessel walls. Spasticity and hypertonicity, no matter how severe, are amenable to therapy. Fibrotic scarring and replacement of degenerated muscle cells are not amenable to therapy, but represent permanent injury.

The degree of relaxability can be easily and rapidly determined by noting the response of the arterial tension to the inhalation of amyl nitrite. The type of response encountered has proved of great assis-

tance in properly evaluating the individual prognosis. In fifty instances, only one incorrect preliminary prognostic opinion was given. Relaxability of the arterioles is evidence of vascular disease relatively early in its pathogenic development, whereas the rigid fibrosed arteries of arteriolar sclerosis respond little or not at all. This procedure makes it easier to answer the patient's justified request for specific information relative to his outlook.

PLASMA PROTEINS *

H. J. WIENER, M.D.

AND

R. E. WIENER, Ph.D.

NEW YORK

The source of the plasma proteins, the manner of their entry into the circulation, their life cycle as well as their physiologic functions still remain largely matters of speculation. Recent work on fibrinogen indicates the site of formation of this protein to be almost exclusively the liver.¹ The liver and the intestinal wall, as well as the blood-forming organs have been considered possible sites for the formation of the serum proteins. The liver, blood-forming organs and ductus thoracicus may be considered likely ports of entry of the proteins into the circulation. It must be conceded that any change in endothelial permeability may have an influence on the protein concentrations of the plasma. In how far the concentrations of the main fractions of the serum proteins and of the plasma fibrinogen reflect the cellular permeability of the organism as a whole or in part is speculative.

This communication deals with the determinations of the two main groups of the serum proteins, the albumin and globulin fractions, together with the plasma fibrinogen, cholesterol, calcium and some of the other blood constituents significant to the clinical condition studied. The pathologic conditions here reported include diabetes mellitus, benign glycosuria, localized and generalized infections, diseases of the liver and gallbladder, acute nephritis, chronic nephritis and nephrosis.

The proteins were separated by fractional precipitation of the plasma, and the nitrogen was determined by the Kjeldahl method and nesslerization. Magnesium sulphate was used for the precipitation of the globulin fraction and fibrinogen of the plasma, and the albumin was determined on this filtrate. The globulin was determined by the difference between the total serum protein determination on the defibrinated plasma and the albumin concentration. The plasma was defibrinated by coagulation through addition of calcium and separation of the fibrin in the clot.

The chemical method of fractional precipitation and determination of the separated fraction is the most reliable of the various methods. While the separation of the two groups of proteins by fractional pre-

* Submitted for publication, Dec. 11, 1929.

1. Howe, Paul E.: The Function of the Plasma Proteins, *Physiol. Rev.* **5**: 439, 1925.

cipitation is not chemically ideal, it does yield more reliable results than the other methods, especially in pathologic conditions, in which variations in other blood constituents are apt to occur. If the concentration of the fraction is determined from a combination of refractometric and viscosity measurements of the serum, the influence of the lipid fraction on the viscosity measurements will often cause an apparent increase in the globulin fraction. Furthermore, variations in the concentrations of other constituents not only may influence the viscosity measurements, but may cause an appreciable error in the refractive index measurement.¹ When a comparison between the total proteins of the serum, determined by refractometric measurement and the Kjeldhal method is made, it must be remembered that the factor of 6.25 by which the nitrogen determined is multiplied to give the protein represented does not equally apply to the two fractions. Nevertheless, the influence of other serum constituents may be seen in the variations of total protein determined by these two methods. The difference in the results as determined by the two methods may vary between 5 and 50 per cent in pathologic conditions.² The agents used for the fractionation of the two groups of proteins and whether the determinations were made on plasma or serum should always be stated. A certain time must necessarily elapse to allow clotting and retraction of clot, if serum is used. Resulting changes in acidity as well as enzymatic activities may result in changes in the protein concentration or in the relative concentrations of the fractions brought about by changes in their physical properties or by stereoconfiguration changes.³ The cholesterol was determined by a modified Bloor method and the calcium by a modification of the usual oxalate method.

The physiologic concentrations of the plasma proteins determined by the methods described on twenty healthy adults are given in table 1.

No difference between the sexes was found in the serum proteins, but a difference in the fibrinogen content of the plasma was noted. The variations in the plasma protein concentrations of the same subject during the year are slight; they tend to be greater in the female. The greatest variations occur during the menstrual period. The differences between the determinations made on the first day of menstruation and

2. Atchley, Dana, W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. M.: Physical and Chemical Studies of Human Blood Serum, *Arch. Int. Med.* **31**:606 (April) 1923.

3. Howe (footnote 1). Petschacher, L.: Spezifische Viscositatserhoehung und Kolloidzustand der Serum Eiweisskoerper, *Ztschr. f. d. ges. exper. Med.* **47**:325, 1925. Kimura, S.: Beitrage zur Kenntnis der Serum Protease. X Mitteilung. Ueber die Mehrheit der Serumprotease, nebst Bemerkungen zur Differenzierung und Charakterisierung der verschiedenen Serumproteasarten, *Tohoku J. Exper. Med.* **7**:561, 1926.

the eighth day in ten cases, calculated on the concentrations determined on the first day, averaged 8 per cent for the albumin fraction, 18 per cent for the globulin fraction and 14 per cent for the fibrinogen. The greatest variations found were: albumin, 15 per cent; globulin, 30 per cent and fibrinogen, 25 per cent. It is therefore prudent to avoid making determinations during this period. The serum protein concentrations during the course of five tests for sugar tolerance were also determined. The fluid intake in these tests was 500 cc. The variations in the total proteins as a rule were within 10 per cent; in only one case was an increase above that encountered (15 per cent). The patients in these cases were normal in respect to their protein concentrations. The average variation in the albumin was 10 per cent and that of the globulin fraction 20 per cent. It has been stated that variations due to food or fluid intake do not exceed 10 per cent.⁴ Results of repeated analyses on healthy adults indicate that a plus or minus variation of 10

TABLE 1.—*Physiologic Concentrations of Plasma Proteins in Twenty Normal Adults*

	High, per Cent	Low, per Cent	Average, per Cent
Total serum protein.....	6.90	5.60	6.40
Serum albumin	5.00	4.20	4.60
Serum globulin	1.90	1.50	1.70
Plasma fibrinogen (male).....	280 mg.	220 mg.	250 mg.
Plasma fibrinogen (female).....	330 mg.	250 mg.	280 mg.
Albumin-globulin quotient	2.2 to 3.3, average 2.7		
Globulin-fibrinogen quotient (male).....	5.2 to 7.6, average 6.8		
Globulin-fibrinogen quotient (female).....	5 to 7, average 6.2		

per cent should be considered within the normal limits. All the analyses reported in this paper were made with the subject in a morning fasting condition, unless otherwise stated.

Table 2 shows the analyses of the proteins in fifteen cases of diabetes mellitus. The corpuscular volume, blood sugar and urine sugar at the time are also reported. The plasma cholesterol and plasma calcium were determined in fourteen of the cases.

The serum protein concentrations in uncomplicated cases of diabetes mellitus are within the normal limits. The albumin-globulin quotient is increased in cases 5, 8, 11 and 15. The high albumin-globulin quotients in case 5 (5.4 and 4.6) are due to an abnormally increased albumin with the globulin concentration reduced below the normal limit. This patient, extremely neurotic, had a tremor, and an increased pulse rate, but a normal basal metabolic rate. In case 8, the albumin-globulin quotient was 4; the albumin concentration was nor-

4. Adler, A.: Die physiologischen Schwankungen des Mischungsverhältnisses von Albumin und Globulin im menschlichen Blutserum, Deutsches Arch. f. klin. Med. **126**:61, 1918.

TABLE 2.—*Diabetes Mellitus*

Case	Date	Sex	Per Cent Serum			Albumin- Globulin Quo- tient	Cell Volume, Cent	Mg. per 100 Cc. Plasma			Glob- ulin- Fibrino- gen Quotient 100 Cc.	Sugar		Comment
			Albu- min	Glob- ulin	Total Protein			Fibrino- gen	Cal- cium	Choles- terol		Blood, Mg. per 100 Cc.	Urine at Time	
1	6/ 9/24 10/13/24 1/19/25	F	5.00 4.82 4.17	1.50 1.58 1.68	6.50 6.40 5.85	3.3 3.0 2.5	40.0 47.0 43.5	244 288 9.2 ...	153	6.2 5.3 ...	222 245 230	0 0 0	
2	5/ 6/24 2/ 1/25	F	4.56 4.35	2.12 1.67	6.68 6.02	2.2 2.6	... 43.5	... 371	9.6	200 226	0 0	
3	5/ 9/27	F	4.80	1.70	6.50	2.8	41.0	230	10.1	222	5.8	230	0	
4	4/27/27	M	4.31	1.81	6.12	2.4	36.5	263	...	170	6.9	170	0	
5	4/12/24	F	5.96	1.11	7.07	5.4	...	454	10.1	...	2.4	222	+++	On treatment with insulin; tremor; increased pulse rate; basal metabolic rate normal
	6/ 4/24		6.35	1.38	7.73	4.6	50.0	345	...	228	4.0	282	++++	
6	5/ 7/24 6/24/24 6/ 2/26	F	4.78 4.70 3.70	1.73 1.83 1.60	6.51 6.54 5.30	2.7 2.6 2.3	46.0 45.6 39.0	... 345 263	10.4 10.1 10.3 230	... 5.3 6.0	138 333 360	+/- +++ +++	On insulin 2 1/4 hours after lunch 2 hours after lunch
7	6/ 1/27	F	4.52	1.67	6.20	2.7	39.3	372	10.3	313	4.6	287	++++	3 hours after breakfast
8	3/31/27	F	4.33	1.09	5.42	4.0	36.3	338	10.5	214	3.2	325	+	Goiter; obesity; normal basal metabolic rate
9	6/ 9/24 5/23/26	F	5.22 5.06	2.45 1.55	7.67 6.61	2.2 3.2	37.7 ...	455 330	9.7 ...	223 230	5.4 4.7	182 333	+/- +++	Rheumatic pains Feels well (2 hours after lunch)
10	11/22/26 4/23/27	M	3.93 4.05	1.78 2.13	5.71 6.18	2.2 1.9	40.7 36.3	330 340	9.6 9.2	412 420	5.4 6.3	147 204	0 0	Edema
11	5/18/25	M	4.80	1.05	5.85	4.6	35.6	412	10.6	175	2.5	156	+/-	Exophthalmos
12	4/21/26	F	5.90	2.82	8.72	2.1	12.0	200	...	154	0	Hypertension
13	7/ 7/24	F	5.64	1.53	7.22	3.6	37.5	...	9.8	125	0	
14	10/ 6/25	M	5.20	2.10	7.30	2.3	38.2	260	...	236	8.0	155	0	
15	1/27/27 3/14/24	M	6.38 3.80	0.92 2.28	7.30 6.08	7.0 1.7	45.0 36.3	262 300	9.3 ...	244 170	3.5 7.6	90 119	0 0	Exophthalmic goiter Bronchitis, fever

mal, but the globulin concentration was decreased (1.09 per cent). This patient had a goiter but a normal basal metabolic rate. The patient in case 15 had exophthalmic goiter and glycosuria; the albumin-globulin quotient was 7 on his first visit. The albumin concentration was increased (6.38 per cent), and the globulin concentration was decreased (0.92 per cent). Six weeks later, during a period of acute infection of the respiratory tract, bronchitis with fever, the albumin concentration was 3.80 per cent, the globulin concentration was 2.28 per cent and the quotient was reduced to 1.7. Evidence of hyperglycemia later proved this case to be one of mild diabetes.

The influence of slight infections such as a cold or sore throat on the serum proteins may also be noted in cases 6 and 9. The patient in case 6 showed a decreased albumin concentration during a period of "cough and cold." In case 9 the globulin concentration decreased with the disappearance of signs of infection from a level of 2.45 per cent to a normal concentration.

Table 3 shows the analyses in six cases of benign glycosuria, some of which have been followed for a period of more than four years. Case 1 may be termed a borderline case in that the blood sugar, when the patient was not in a fasting condition, rose slightly above normal. The protein concentrations in all these cases were within the normal limits. The average concentrations were: albumin, 5.4 per cent and globulin, 1.64 per cent, the average quotient was 3.1. The average concentrations in the uncomplicated cases of diabetes mellitus were: albumin, 4.84 per cent; globulin, 1.74 per cent and the average quotient 2.8. There is practically no difference in the serum protein concentrations between the cases of "renal glycosuria" and the cases of diabetes mellitus. The plasma calcium concentration in the cases of renal glycosuria, just as in the majority of cases of uncomplicated diabetes mellitus, tends toward the high normal limit or is even slightly increased.

Table 4 gives the analyses in forty cases of either localized or generalized infections. Nineteen of the cases reported were cases of diabetes. The average protein concentrations in the diabetic cases were: albumin, 3.57 per cent; globulin, 2.68 per cent and fibrinogen, 620 mg. per hundred cubic centimeters. The same consistently lowered albumin concentration, increased fibrinogen and increase in the globulin concentration in the more severe cases is shown in the other cases uncomplicated by diabetes mellitus. The average concentrations in these cases were: albumin, 3 per cent; globulin, 3.17 per cent, and fibrinogen, 570 mg. per hundred cubic centimeters. The degree of variation from the normal in the two fractions of the serum proteins corresponds to the severity of the clinical condition. The progressive drop in the albumin-globulin quotient, mainly due to an increase in the globulin fraction, is well shown in cases 38, 39 and 40.

TABLE 3.—*Benign Glycosuria*

Case	Date	Sex	Per Cent Serum			Albumin- Globulin Volume,		Mg. per 100 Cc. Plasma			Glob- ulin-	Sugar		Comment
			Albu- min	Glob- ulin	Total Protein	Quo- tient	per Cent	Fibrino- gen	Cal- cium	Choles- terol	Fibrino- gen	Blood, Mg. per Quotient 100 Cc.	Urine at Time	
1	1/ 8/25	F	4.60	1.90	6.40	2.4	44.0	9.3	256	436	4.4	138	4.3%	First day of menses (2 hours after breakfast)
	1/21/25		4.05	2.44	6.49	1.7	37.3	9.7	...	248	9.9	111	2.3%	Tonsillitis
	4/30/25		3.70	2.05	5.75	1.8	45.0	...	192	149	3.3%	Leukorrhea (not fasting)
	4/11/27		3.62	2.03	5.65	1.8	43.3	...	178	293	7.2	107	5.0%	
	4/25/27		4.30	1.76	6.06	2.4	38.0	269	6.5	105	4.2%	First day of menses
2	2/ 6/24	F	6.26	1.31	7.58	4.8	10.3	...	372	3.5	111	++	First day of menses; 3 hours after lunch; enlarged tonsils
	2/13/24		5.50	1.89	7.39	2.9	10.9	192	415	4.5	89	++	
	4/14/24		6.12	1.94	8.06	3.2	11.0	111	++	Not fasting
	4/28/24		5.22	1.94	7.16	2.7	43.0	10.5	100	1.7%	
	5/ 5/24		5.05	1.84	7.49	3.1	50.5	10.4	...	440	4.2	121	1.8%	Not fasting
3	4/15/25		5.23	1.00	6.23	5.2	41.5	324	3.1	95	+++	
	3/28/27		4.50	1.33	5.88	3.2	38.1	...	167	247	5.6	105	1.7%	Tonsillectomy in September, 1926
	5/ 1/25	M	5.80	1.60	7.40	3.6	46.5	...	133	133	++	Boy, aged 11; 2 hours after lunch
	5/29/25		4.83	1.91	6.74	2.5	47.0	10.7	170	93	++	
	12/21/26		3.90	1.00	4.90	3.9	46.0	...	85	156	6.4	106	2%	Extremely obese (3 hours after lunch)
4	4/22/27		4.50	1.80	6.16	2.4	40.5	...	150	373	4.8	110	2%	Less obese (3 hours after lunch)
	4/ 4/27	M	4.13	2.02	6.15	2.0	48.0	246	8.2	113	1.2%	3 hours after lunch
	4/15/27		4.50	1.62	6.12	2.8	44.5	...	150	253	6.4	100	1.5%	
5	5/18/25	M	4.60	1.90	6.50	2.4	49.2	10.1	...	269	7.0	104	+	
6	6/15/24	M	5.00	2.18	7.18	2.4	42.5	...	138	245	8.9	117	+	Not fasting

TABLE 4.—*Localized and Generalized Infections*

Case	Date	Sex	Per Cent Serum			Albumin- Globulin Quo- tient	Cell Volume, Cent	Mg. per 100 Cc. Plasma			Glob- ulin- Mg. per 100 Cc. Blood			Comment
			Albu- min	Glob- ulin	Total Protein			Fibrino- gen	Choles- terol	Cal- cium	Fibrino- gen	Non- protein Nitro- gen	Uric Acid	
1	1/5/26	M	2.46	1.89	4.35	1.3	33.0	515	104	...	3.7	39	...	Gangrene; diabetes mellitus
2	2/8/26	M	3.16	2.10	5.26	1.5	24.5	750	103	...	2.8	50	2.9	Gangrene; diabetes mellitus
3	1/15/26	M	3.85	2.15	6.00	1.8	33.0	435	167	...	4.8	Gangrene; diabetes mellitus
4	1/20/26	M	3.25	2.17	5.42	1.5	23.5	900	185	...	2.4	30	...	Gangrene; diabetes mellitus
5	2/15/26	M	2.76	2.52	5.28	1.0	22.0	780	144	...	3.6	Gangrene; diabetes mellitus
6	3/5/26	M	3.25	1.89	5.14	1.7	45.3	340	115	...	5.6	Gangrene; diabetes mellitus (post operation)
7	9/8/25	F	3.20	3.49	6.75	0.9	38.0	433	5.8	...	3.0	Gangrene; diabetes mellitus (ambulant clinic ease)
8	2/19/26	M	2.19	2.31	4.50	1.0	10.3	550	130	...	4.2	38	4.2	Gangrene; diabetes mellitus (ambulant clinic ease)
9	1/19/26	M	3.37	3.57	6.94	0.9	38.0	175	...	10.2	7.1	48	4.5	Appendicitis; diabetes mellitus
10	2/28/24	M	4.30	2.38	6.68	1.8	...	590	...	11.3	4.0	Infected toe; diabetes mellitus
11	7/28/27	F	3.00	2.38	5.38	1.3	30.4	578	76	...	4.1	21	...	Infected finger; diabetes mellitus; beginning erysip- elas
12	8/5/27	F	3.35	2.58	5.93	1.3	35.7	880	160	...	2.9	30	...	Has had two injections of erysipelas antitoxin; recovered
13	12/27/25	F	3.64	2.66	6.30	1.4	36.5	600	136	...	4.4	30	2.0	Infected hand (Staphylococcus aureus)
14	5/11/27	F	3.59	2.89	6.48	1.5	...	447	...	9.3	5.4	Ulcer of leg; diabetes mellitus
15	5/21/27	M	3.95	2.21	6.16	1.8	37.2	462	5.3	Furunculosis; diabetes mellitus
16	11/20/27	F	2.85	2.25	5.10	1.3	36.2	625	250	...	3.6	23	5.3	Temporal furuncle
17	1/6/27	F	2.37	2.59	4.96	0.9	15.6	600	304	9.1	4.3	130	...	Infection post currtage; anuria
18	4/13/27	F	4.00	2.84	7.74	1.7	36.0	568	5.0	✓ Tuberculosis, pulmonary; diabetes mellitus
19	8/20/27	F	2.85	2.31	5.16	1.2	33.6	461	120	...	5.0	Pleurisy; diabetes mellitus
20	8/30/27	F	2.46	3.24	5.70	0.8	30.0	565	146	...	5.7	No infection
21	7/15/29	F	4.25	1.81	6.06	2.4	36.1	197	150	...	9.2	25	...	Tuberculosis, pulmonary
22	8/8/27	F	3.69	2.54	6.23	1.5	36.0	650	91	9.6	3.9	29	...	Bronchitis
23	7/15/27	F	2.71	3.89	6.60	0.7	41.6	900	4.3	Tuberculosis, arrested pulmonary; ieteric index 12
24	6/15/26	M	4.19	2.54	6.73	1.7	38.7	354	...	9.6	7.2	Ieteric index 12
25	11/5/27	M	3.75	2.10	5.83	1.8	45.6	278	288	9.5	7.4	40	...	Ieteric index 14
26	5/6/29	M	2.85	2.10	4.95	1.4	44.8	272	112	10.2	7.4	24	...	Infectious asthma
27	2/3/25	F	1.67	2.89	4.58	0.6	46.6	526	111	...	5.5	42	3.1	Colitis; ieteric index 8
28	2/8/26	F	3.74	2.30	6.04	1.6	38.8	625	163	...	3.7	40	1.6	Cystitis; prostatitis
29	2/13/26	M	2.70	2.36	5.06	1.1	19.6	422	98	10.5	5.7	52	5.7	Cystitis, postoperative for gangrene; diabetes mellitus
30	8/10/27	M	2.81	2.06	4.87	1.4	32.9	923	267	...	2.2	25	...	Cystitis; postoperative for gangrene; diabetes mellitus
31	12/25/26	M	3.66	3.11	6.77	1.2	28.3	616	177	...	5.0	36	2.1	Cystitis; post suprapubic cystostomy
32	2/27/26	M	1.96	2.04	4.00	1.0	20.1	570	76	...	5.1	40	3.7	Cystitis; postoperative for bladder stone
33	3/1/26	M	2.33	3.66	5.98	0.6	31.0	643	85	...	4.0	56	4.4	Cystitis; prostatitis
34	3/8/26	F	2.94	2.88	5.82	1.0	22.7	715	142	9.2	3.3	33	4.1	Pyelitis

29	5/17/27	F	2.92	2.61	5.53	1.1	31.0	800	127	...	2.4	25	1.5	...	Pyelitis; five months pregnant
30	5/17/27	F	3.72	2.48	6.20	1.5	36.7	1,040	138	...	2.4	38	Pyelitis; five and a half months pregnant
31	3/14/27	M	3.45	2.08	5.53	1.7	...	322	180	9.4	6.4	25	Syphilis, tertiary; post recovery from arsphe- nine jaundice
32	6/18/24	F	4.20	3.60	7.80	1.2	39.2	610	162	...	5.9	121	Syphilis, tertiary; diabetes mellitus
	6/11/26		5.21	3.85	8.89	1.4	32.0	625	230	...	5.9	122	
33	3/ 1/27	F	3.13	2.35	5.48	1.3	36.5	575	230	...	4.1	25	...	438	Syphilis, tertiary; diabetes mellitus
34	8/25/27	F	3.51	2.76	6.30	1.3	28.5	750	157	...	3.6	400	Syphilis, tertiary; diabetes mellitus; perforating ulcer
35	3/12/26	M	3.12	4.09	7.20	0.8	37.9	...	146	9.5	...	25	1.5	...	Syphilis, tertiary
36	2/ 5/20	F	4.36	3.06	7.41	1.4	42.3	416	104	9.6	7.4	25	Syphilis, tertiary
37	6/25/27	F	3.00	3.68	6.68	0.8	23.4	852	100	10.1	6.4	28	4.3	...	Pyelitis; five and a half months pregnant
38	12/22/24	F	2.58	1.43	4.01	1.8	371	269	3.8	28	3.9	...	Syphilis, tertiary; seven and a half months preg- nant; chronic nephritis; hypertension
	1/25/25		2.87	1.88	4.75	1.5	24.5	657	2.9	31	6.1	...	Last of ten treatments with arsphe- namine, Jan. 10
	1/30/25		3.83	3.05	6.43	1.1	33.6	800	335	8.8	3.8	46	7.3	...	Blood pressure 170/110
	2/16/25		3.78	3.79	7.56	1.0	35.0	666	...	9.0	5.7	43	5.0	...	Delivered of a living infant twelve days later
	3/26/25		2.75	2.90	4.65	1.0	30.0	702	193	8.8	4.2	54	5.9	...	Tubo-ovarian abscess
	5/11/25		2.41	3.26	5.70	0.8	23.4	577	99	...	3.0	40	6.1	...	High fever; colpotomy 4/21; transfusion 4/24
	6/ 8/25		2.03	4.47	6.50	0.5	23.3	636	153	12.4	7.0	40	6.1	...	Fever; cystitis; profuse vaginal discharge; blood pressure 130/90
	6/30/25		3.52	3.61	7.13	1.0	28.4	676	214	13.6	5.3	51	8.1	...	Cystitis; vaginal discharge; fever
	7/15/25		2.93	5.67	8.25	0.5	26.8	600	182	11.6	9.4	34	6.0	...	Cystitis; vaginal discharge; fever
	10/ 1/25		2.92	5.17	7.79	0.5	36.8	448	214	...	11.6	64	Cystitis and profuse vaginal discharge
	10/15/25		3.05	2.53	5.63	1.2	31.8	432	200	10.1	6.0	55	5.4	...	Blood pressure 150/112; creatinine (blood) 2 mg. per hundred cubic centimeters
	1/11/26		2.82	2.93	5.75	1.0	35.0	507	240	...	5.8	40	3.9	...	Increasing hypertension; blood pressure 170/105
	3/15/26		3.09	2.61	5.70	1.2	...	350	153	10.1	7.4	41	4.3	...	Blood pressure 190/135
	4/12/26		3.05	2.45	5.50	1.2	35.0	440	5.5	44	2.1	...	Blurred vision; blood pressure 190/136
	6/ 2/26		2.71	2.22	4.96	1.2	35.0	290	272	13.2	7.7	64	3.5	...	Died in pseudo-uremic coma
	6/ 4/26		2.83	2.03	4.91	1.4	28.1	347	...	8.2	5.9	55	
39	1/27/26	M	2.91	3.82	6.76	0.8	19.1	505	139	9.4	7.6	33	3.6	...	Acute leukemia; icteric index 6
	2/ 1/26		2.45	6.78	9.21	0.4	18.0	750	155	...	9.0	41	3.8	...	Icteric index 9; died ten days later
40	5/24/24	F	4.81	2.01	6.88	2.4	44.5	277	...	10.5	7.4	25	2.0	...	No complaints except slight tenderness in right hypocondrium region
	6/17/25		3.80	1.97	5.77	1.9	42.0	338	208	...	5.7	30	Chills; nausea; pain in right hypocondrium region; icteric index 13
	6/26/25		3.58	3.32	6.90	1.1	40.0	385	8.6	Agranulocytic angina, first symptoms 6/23; bili- rubin 1.7 mg. per hundred cubic centimeters
	7/ 8/25		3.21	4.26	7.50	0.8	833	112	9.8	5.1	22	3.0	...	Direct van den Bergh positive; bilirubin 2 mg. per hundred cubic centimeters
	7/10/25		2.28	6.32	8.60	0.4	867	120	9.3	7.3	35	2.3	...	Icteric index 54; bilirubin 4.8; direct van den Bergh positive; died four days later

One patient (case 38), treated for syphilis and nephritis, was followed through a pregnancy and after delivery of a living infant, to death sixteen months later. The albumin-globulin quotient showed a decrease from the seventh month of pregnancy on, when syphilitic treatment was discontinued. The decrease in the quotient was mainly due to an increase in the globulin fraction, which gradually rose from a level of 1.43 to 3.78 per cent at term. The albumin fraction increased slightly during this time. The increase in fibrinogen was greater than that normally seen in pregnancy. A tubo-ovarian abscess developed four weeks after delivery. The patient ran an intermittent temperature, occasionally up to 104 F. Colpotomy was performed, and this was followed by a transfusion. The elevation in temperature continued intermittently for more than two months. The patient was discharged from the hospital three months after delivery, but cystitis and profuse vaginal discharge continued for more than four months. The albumin-globulin quotient decreased progressively after delivery (in February) and remained at an extremely low level until October. During this time the globulin concentration increased considerably, occasionally rising to a level of more than 5 per cent. During September and October the patient was given four treatments with neoarsphenamine, and her condition improved. The albumin-globulin quotient rose from a level of 0.5 to 1.2. At the beginning of June the following year she reported to the clinic with blurred vision, headaches and marked hypertension. Two days later pseudo-uremic convulsions and coma set in, and the patient died within twelve hours. The terminal azotemia was little increased beyond the limits observed in this patient before. There were no terminal changes in the serum protein concentrations.

Case 40 was a rapidly fatal case of agranulocytic angina. The first analysis shown (May 24, 1924) was made before the onset of the illness. In June of the following year the patient complained of abdominal pain and slight fever. Analysis of the blood on June 17 showed lowered albumin, increased globulin, increased fibrinogen, increased bilirubin and a slightly delayed, positive direct van den Bergh reaction. Nine days later (June 26) the globulin content of the serum had almost doubled. On June 28 the first symptoms of agranulocytic angina developed, ulceration of the mouth and a beginning leukopenia. The rise in the globulin continued, and fulminating sepsis with progressively increasing leukopenia led to her death seventeen days later. Four days before death the globulin concentration was 6.32 per cent.

The condition in case 39, acute leukemia, also presented the picture of a severe infection. The globulin, eleven days before the patient's death, rose to 6.78 per cent. The fibrinogen was 750 mg. per hundred cubic centimeters, and the albumin was materially decreased.

In infections showing clinical signs and symptoms the globulin is increased, and this increase seems to parallel the severity of the condition. The albumin is decreased, markedly so in the more severe conditions. The fibrinogen is increased and may show a decided increase in the milder conditions, which show no effect on the globulin concentration.

Table 5, analyses in twenty-three cases, shows the disturbed protein relationship in hepatic cirrhosis (twelve cases), cholecystitis (four cases), jaundice (four cases) and jaundice due to the use of Arsphenamine (three cases).

In these cases the parallelism between the severity of the condition and the decrease in the albumin-globulin quotient due to a decrease in albumin and an increase in globulin is also noted. The variations from the normal, however, are generally not so marked as those in the more severe infectious conditions shown in table 4.

In the cases of hepatic cirrhosis the changes in the fibrinogen concentrations as compared to the changes in the albumin and globulin concentration differ fundamentally from the observed changes in infectious conditions. In the infectious conditions, uncomplicated by a liver deficiency, the fibrinogen is always increased, the albumin is decreased and the globulin is increased in the more severe conditions only. In cirrhosis of the liver the albumin is decreased, the globulin is normal or moderately increased, but the fibrinogen remains within the normal limits or is even decreased below the normal concentration. In the infectious conditions the fibrinogen is always increased; in cirrhosis of the liver the fibrinogen will decrease with the progressive severity of the condition. The globulin increases while the fibrinogen remains within the normal limits or is even decreased.

The first analysis in case 8 shows the blood chemistry before the onset of clinical symptoms of hepatic cirrhosis. A moderate chronic sinusitis was responsible for the increased fibrinogen (402 mg. per hundred cubic centimeters) and cholesterol. The urine gave a two plus urobilinogen reaction, testifying to a slight liver insufficiency, and this may account for the relatively slight rise in the fibrinogen concentration in the presence of the infection. About nine months later, the patient complained of occasional intestinal disturbances with diarrhea. The blood chemistry at that time showed a greatly increased globulin concentration, while the fibrinogen was not materially increased and had actually decreased 10 per cent from the concentration found in the previous analysis. While the globulin had increased from 1.65 to 3.80 per cent, the fibrinogen had decreased from 402 to 360 mg. per hundred cubic centimeters. Three months later the blood chemistry revealed a decided decrease in both serum proteins, and the fibrinogen had decreased to a concentration below the normal, 214 mg. per hundred

TABLE 5.—*Diseases of the Liver and Gallbladder*

Case	Date	Sex	Per Cent Serum			Albu- min- Gloh- ulin- tinent	Cell Vol- ume, per Cent	Mg. per 100 Cc. Plasma		Gloh- ulin- tinent		Mg. per 100 Cc. Blood		Comment			
			Albu- min	Gloh- ulin	Total Pro- tein			Fi- brino- gen	Cho- les- terol	Cal- cium	Cal- cium	Uric Acid	Sugar		Non- protein Nitro- gen	Index	
1	12/15/26	F	2.82	3.53	6.35	0.8	...	300	238	11.8	1.0	133	22	38	Hepatic cirrhosis; acute alcoholism; died one week later
2	1/5/27	M	1.93	1.92	3.85	1.0	22.5	203	109	9.6	2.3	94	24	22	Hepatic cirrhosis; bilirubin, 4.8 mg. per hundred cubic centimeters; direct van den Bergh positive
3	2/1/27	M	2.94	2.46	5.40	1.2	43.0	186	13.2	...	100	35	7	Hepatic cirrhosis
4	1/10/27	M	2.65	4.89	7.54	0.5	40.0	274	223	17.7	4.3	14	Hepatic cirrhosis
5	5/19/27	M	3.58	2.48	6.06	1.5	...	340	192	7.3	6	Hepatic cirrhosis; not definitely diagnosed
6	7/20/27	M	3.45	3.10	6.55	1.1	40.0	472	143	6.6	6.0	100	33	..	Hepatic cirrhosis; alcoholism; syphilis
7	12/1/27	F	3.91	1.96	5.87	2.0	...	420	4.6	4.6	111	25	45	Hepatic cirrhosis; alcoholism
	12/4/27		3.65	2.85	6.50	1.3	36.3	450	91	6.2	2.4	50	Bilirubin, 5.3 mg. per hundred cubic centimeters; direct test positive
	12/14/27		3.96	2.74	5.70	1.1	33.6	348	233	7.9	3.3	98	30	20	Bilirubin, 2.5 mg. per hundred cubic centimeters; direct test very much delayed, positive
	12/21/27		3.14	2.40	5.54	1.3	28.3	300	244	8.0	1.7	89	35	6	Died three months later
8	12/9/26	M	4.20	1.65	5.85	2.6	41.6	402	223	11.2	4.1	3.7	27	..	Chronic mild sinusitis; hypertension; blood pressure 185/110
	10/27/27		4.30	3.80	7.10	1.2	37.5	360	138	...	10.1	4.0	29	..	Loose stools, 5 to 6 daily; stools negative
	1/30/28		3.33	1.15	4.48	3.0	40.5	214	167	9.9	5.4	4.6	30	6	Loose stools; loss of weight; blood pressure 150/80
	3/21/28		2.48	2.82	5.00	1.0	38.1	173	218	...	14.5	4.3	100	23	14	17	Loose stools; edema of ankles
	4/12/28		2.28	2.17	4.45	1.0	35.7	87	125	...	24.8	8.2	26	17	Stools again negative
	4/28/28		2.70	1.60	4.30	1.6	31.7	195	100	9.5	8.2	5.7	160	18	10	10	Small amount of fluid in abdomen; tapped 4/20; injection of emetine hydrochloride
	12/5/28		4.14	1.76	5.90	2.3	45.0	238	96	6.8	2.2	...	25	6	Exploratory 5/3; beginning hepatic cirrhosis; modified
	5/16/29		3.45	1.25	4.70	2.7	50.0	279	121	4.5	3.3	6	Palma operation
																	Has gained weight and feels well
9	4/22/27	F	2.46	3.23	5.69	0.8	21.7	365	190	8.8	3.3	110	28	12	Hepatic cirrhosis; ascitis; Ur. urobilinogen +++
	5/19/27		2.45	2.25	4.70	1.1	21.2	430	223	9.4	5.2	151	25	12	Bilirubin, 0.4 mg. per hundred cubic centimeters; direct van den Bergh negative
	5/27/27		2.65	2.60	5.25	1.0	16.7	343	164	7.6	3.6	150	32	14	Transfused 5/27; chill after transfusion
	6/1/27		2.13	2.77	4.90	0.8	23.5	370	166	8.2	7.5	11.0	110	34	12	12	Bleeding from gums; platelet count, 160,000
	6/15/27		3.12	2.65	5.77	1.2	23.2	388	222	9.3	6.8	6.6	125	23	8	8	Platelet count, 7/5, 12,200; 7/13, 16,000
	7/25/27		2.35	3.14	5.49	0.8	15.2	270	217	8.2	11.6	...	114	22	9	9	Injections of horse serum; platelet count, 8/6, 310,000
	8/11/27		2.95	2.80	5.75	1.0	16.5	191	156	8.5	14.8	7.5	...	26	8	8	Injections of dextrose and insulin
	8/22/27		3.05	3.15	6.20	1.0	16.1	266	136	9.1	11.8	6.0	103	22	7	7	

[illegible]

TABLE 5.—Diseases of the Liver and Gallbladder—(Continued)

Case	Date	Sex	Per Cent Serum			Albu- min- Glo- b- ulin	Cell Vol- ume, Cent	Mg. per 100 Cc. Plasma			Glob- ulin- Fibrino- gen	Glob. Mg. per 100 Cc. Blood			Comment
			Albu- min	Glob- ulin	Total Pro- tein			Fi- brino- gen	Cho- les- terol	Cal- cium		Uric Acid	Sugar	Non- protein Nitro- gen	
19	2/15/27	M	3.76	2.52	6.28	1.6	34.0	440	5.7	100	30	33	Arsphenamine jaundice; gastric ulcer; bilirubin, 1.5 mg. per hundred cubic centimeters
	2/17/27		3.72	3.31	7.06	1.1	38.5	480	7.0	...	36	25	Bilirubin, 1.4 mg. per hundred cubic centimeters; direct van den Bergh delayed
	2/24/27		4.40	3.32	7.72	1.3	43.0	410	8.1	...	36	30	Bilirubin, 1.8 mg. per hundred cubic centimeters; direct van den Bergh delayed
	3/ 5/27		1.31	2.71	7.05	1.6	41.0	375	7.2	...	33	19	Bilirubin, 0.8 mg. per hundred cubic centimeters; direct van den Bergh negative
20	11/23/27	F	2.58	3.52	6.10	0.7	28.7	455	204	...	7.7	5.0	98	20	Arsphenamine poisoning; nephritis; pregnancy; direct van den Bergh delayed
	11/26/27		2.50	3.08	5.66	0.8	16.5	490	262	7.5	6.3	...	165	25	Bilirubin, 1.5 mg. per hundred cubic centimeters; direct van den Bergh slightly delayed; creatinine 6.8 mg. per hundred cubic centimeters
	11/27/27		2.95	3.40	6.35	0.9	20.0	630	290	8.3	5.4	17.3	...	27	Bilirubin, 1.7 mg. per hundred cubic centimeters; direct van den Bergh positive; creatinine, 6.8 mg. per hundred cubic centimeters
	11/30/27		2.09	3.51	5.60	0.6	19.0	513	293	8.5	6.9	16.6	...	25	Bilirubin, 1.7 mg. per hundred cubic centimeters; direct van den Bergh positive in 45 seconds; creatinine, 4.7 mg. per hundred cubic centimeters
	12/ 1/27		2.25	3.11	5.36	0.7	22.0	488	354	...	6.1	23.0	...	25	Bilirubin, 1.7 mg. per hundred cubic centimeters; direct van den Bergh positive in 30 seconds; creatinine, 3.0 mg. per hundred cubic centimeters
	12/ 3/27		2.67	5.04	7.11	0.5	23.0	596	453	9.0	8.5	9.2	...	27	Bilirubin, 2.1 mg. per hundred cubic centimeters; direct van den Bergh positive in 15 seconds; creatinine, 3.0 mg. per hundred cubic centimeters; urine urobilinogen
21	12/22/26	F	3.65	2.60	6.25	1.4	...	735	3.8	...	182	80	Cholecystitis; diabetes mellitus; died 12/7
	1/20/27		3.48	2.97	6.45	1.2	...	345	126	...	8.6	...	126	15	Bilirubin, 12/22, 7.5 mg. per hundred cubic centimeters; 1/20, 2.5 mg. per hundred cubic centimeters; direct van den Bergh negative
	5/15/27		6.20	3.00	9.20	2.1	...	550	5.4	...	143	6	Urobilinogen negative; direct van den Bergh negative
22	1/ 4/26	M	3.12	1.96	5.08	1.6	43.2	1,130	1.7	3.6	133	25	Cholecystitis; cholelithiasis; direct van den Bergh delayed
	1/21/26		5.50	5.96	11.48	0.9	36.0	1,500	3.9	3.2	143	5	One day after operation
	2/ 1/26		3.38	2.10	5.48	1.5	35.2	513	4.1	4.9	150	36	
	3/10/26		2.22	2.60	4.82	0.9	44.7	370	173	...	7.0	...	173	47	Bilirubin, 2 mg. per hundred cubic centimeters; direct van den Bergh negative; glycosuria
23	11/21/27	F	4.44	2.89	7.33	1.5	...	963	3.0	33	Cholecystitis; bilirubin, 1.5 mg. per hundred cubic centimeters; direct van den Bergh positive

cubic centimeters. Physical examination in February showed the upper border of the liver in normal position and the lower border just palpable on deep inspiration only. The urine showed a trace of bile and urobilinogen two plus. Increased intestinal action with loose stools continued, and toward the end of March there was occasionally edema of the ankles. On March 21, the liver was not manifestly enlarged, the spleen was not felt and there was no manifest free fluid in the abdominal cavity. The urine gave a four plus urobilinogen reaction, but in all other respects was normal. The feces on repeated examination were normal. The blood chemistry showed a further decrease in the albumin concentration (2.48 per cent), and the globulin fraction had increased (2.52 per cent). The fibrinogen was still further decreased, 173 mg. per hundred cubic centimeters. X-ray visualization of the gall-bladder with the dye test failed; the gastro-intestinal x-ray series were also negative. On April 21, there was fulness in the abdomen which was tapped. The fluid withdrawn showed the characteristics of a transudate. The test meal showed an absence of free hydrochloric acid. The Wassermann test was twice found negative. On April 12, the albumin was 2.28 per cent, the globulin was 2.17 per cent and the fibrinogen had reached the low level of 87 mg. per hundred cubic centimeters. Injections of emetine hydrochloride were started on April 21 and injections of a bismuth compound on April 29. The blood chemistry on April 29 showed a slight improvement, albumin 2.71 per cent, globulin 1.60 per cent and fibrinogen 195 mg. per hundred cubic centimeters. An exploratory operation was performed on May 3. There were then several liters of fluid in the abdominal cavity. The liver was slightly enlarged, was hard and had a granular surface. Microscopic examination of a small piece removed showed beginning portal cirrhosis. A modified Talma operation was done. The patient since discharge from the hospital has gained weight, feels well and has been attending to his professional duties. In December of the same year his serum protein concentrations were normal, the albumin-globulin quotient was 2.3, and the fibrinogen concentration was 238 mg. per hundred cubic centimeters. In May, 1929, the serum proteins while slightly below normal gave an albumin-globulin quotient of 2.7, and the fibrinogen had risen to 279 mg. per hundred cubic centimeters.

Case 9 was followed for a period of seventeen months. When first seen the liver was markedly enlarged, and the spleen was moderately enlarged. There were subicteric sclerae and emaciation. The urine gave a four plus urobilinogen reaction. On the first analysis the albumin was 2.46 per cent, the globulin 3.23 per cent and the fibrinogen 365 mg. per hundred cubic centimeters. On rest in bed the albumin-globulin quotient improved somewhat, due to a decrease in the globulin concentration. The fibrinogen rose to 430 mg. per hundred cubic centi-

meters. This is the highest fibrinogen concentration found during the course of this illness, which ended in death seventeen months later. During a time of considerable prostration and bleeding from the gums, the fibrinogen was reduced to 191 mg. per hundred cubic centimeters while the globulin was increased above the normal concentration. The patient was given injections of dextrose and insulin and afterward insulin treatment, 10 units twice daily. There was considerable transient improvement, so that she was able to leave the city for the seashore toward the end of the summer. This improvement was accompanied by a slight rise in the albumin and fibrinogen concentration and a fall in the globulin concentration. In the late fall she was still further improved. At that time the albumin was 4.18 per cent, the globulin 1.57 per cent and the fibrinogen 265 mg. per hundred cubic centimeters, i. e., below the normal. In January the following year ascitis developed, which necessitated increasingly frequent tapping from then on. The decline was gradual, interrupted by slight transient improvements. On May 2 the globulin had again risen to 2.4 per cent with a fibrinogen slightly below the normal limit. The albumin had decreased to 1.98 per cent. The tendency to bleeding was then being controlled by injections of fibrogen. The patient died six months later.

The changed relationship between fibrinogen on the one hand and albumin and globulin on the other is also shown in case 10, that of a man, aged 52 years, with hepatic cirrhosis, diabetes mellitus and dental abscesses. The influence of a concurrent infection on the fibrinogen and globulin concentrations is well illustrated by this case. The dental infection was severe, three of the teeth being abscessed. The albumin at the time of the first visit was 2.66 per cent, the globulin 4.68 per cent and the fibrinogen concentration within the normal limits, 280 mg. per hundred cubic centimeters. Rest in bed and treatment with insulin for the diabetes mellitus brought about clinical improvement. The hypertension found on the first visit decreased, and the liver decreased in size. The globulin concentration gradually was lowered to 3 per cent, while the fibrinogen increased to 380 mg. per hundred cubic centimeters. The blood chemistry during this time reflected the clinical condition. An acute intestinal upset promptly caused a rise in the globulin to as high as 4.43 per cent. Four days following the extraction of the infected teeth, while the healing process of the gums was not complete, there was a drop in the fibrinogen (247 mg. per hundred cubic centimeters), while the globulin had slightly increased (from 3.15 to 3.45 per cent). Four weeks later, when the gums had completely healed, the globulin was 2.62 per cent, the albumin had increased to 3.13 per cent (from 2.40 per cent) and the fibrinogen was 255 mg. per hundred cubic centimeters. This case illustrates the inability of the diseased liver to respond to the

irritation caused by an infection as expressed by the fibrinogen concentration. The fibrinogen failed to rise proportionately, while the rise in the globulin exceeded that expected from the nature of the infection.

The average protein concentrations in the first nine cases of hepatic cirrhosis were: albumin, 3.15 per cent; globulin, 2.57 per cent; fibrinogen (male), 254 mg. per hundred cubic centimeters; (female), 324 mg. per hundred cubic centimeters. The average protein concentrations in case 10 while the infection persisted were: albumin, 2.55 per cent; globulin, 3.40 per cent and fibrinogen (male) 319 mg. per hundred cubic centimeters.

The five cases of jaundice without elevation of temperature (12—16) had a total protein concentration approaching the high normal limit. The albumin fraction was slightly decreased and the globulin fraction was somewhat increased. The average albumin-globulin quotient in these cases was 1.6. The fibrinogen was normal or slightly increased. In case 16 the patient had a decided jaundice on her first visit (icteric index 60, direct van den Bergh positive in one minute, bilirubin by indirect method 5.5 mg. per cent). The jaundice gradually subsided, and fourteen days later the icteric index was 20. The blood chemistry on the first analysis showed a greatly reduced albumin concentration, (2.74 per cent), normal globulin and reduced fibrinogen (220 mg. per hundred cubic centimeters). On her second visit the albumin had increased to 3.53 per cent, the globulin had more than doubled (3.61 per cent), while the fibrinogen remained practically the same. Five days later the total protein concentration was found to be 5.75 per cent, and the fibrinogen had increased to normal concentration. As the jaundice cleared up, the albumin-globulin quotient returned to normal, though the serum proteins were below the normal concentration, especially the albumin fraction. In case 14 the same phenomenon of an increase in the globulin concentration shortly after the jaundice developed with a return to normal as the jaundice cleared up, is to be observed. This was a case of consistent urobilinogenuria, and the decline in the total serum protein concentration as well as in the fibrinogen concentration found sixteen months later would indicate an increase in the liver insufficiency.

The insufficient response to an infection by the liver as expressed by the fibrinogen concentration is also shown in the cases of jaundice due to the use of arsphenamine and the case of arsphenamine poisoning. In the two cases of jaundice due to the use of arsphenamine the fibrinogen was below the level usually found in syphilis. In case 20 is reported rapidly fatal arsphenamine poisoning during pregnancy, complicated by nephritis. The fibrinogen was not increased beyond the limits usually found during the later months of a normal pregnancy. The albumin-globulin quotient on the day of admittance was 0.7, owing

to a much decreased albumin and increased globulin. The quotient decreased to 0.5, and the globulin rose from 3.52 on the day of admission to 5.04 per cent.

In case 21, that of a woman with mild diabetes and a definite cholecystitis, the fibrinogen was markedly increased, the albumin was decreased and the globulin was above the normal limit. The bilirubin was 7.5 mg. per hundred cubic centimeters, and the direct van den Bergh reaction was positive. The urine showed a three plus urobilinogen reaction. Five months later, when the patient had completely recovered from the jaundice, the serum proteins were much increased with a normal albumin-globulin quotient. The patient in case 22, an operative case of cholelithiasis and cholecystitis, showed this transient rise in the serum proteins, intensified by the effects of the anesthesia, in an exaggerated form. Two weeks before the operation the blood chemistry showed a decreased albumin concentration, high normal globulin and a much increased fibrinogen concentration (11.30 mg. per hundred cubic centimeters). The day following the operation the serum proteins were 11.48 per cent (albumin 5.50 per cent, globulin 5.96 per cent), and the fibrinogen had increased to 1,500 mg. per hundred cubic centimeters. Ten days later the analysis gave normal total protein with the albumin fraction slightly below normal and the globulin somewhat increased. The albumin-globulin quotient was 1.5. The fibrinogen was 513 mg. per hundred cubic centimeters. Seven weeks later, after the patient had left the hospital, the icteric index had again risen to 20, glycosuria had developed and the total proteins were reduced below the low normal limit. There was a further decrease in the albumin fraction, while the globulin had risen to 2.60 per cent. The fibrinogen was 370 mg. per hundred cubic centimeters. This unfavorable analysis was reflected by the clinical condition.

Number 1 in table 6 is a case of myelogenous leukemia in a woman, aged 47, who was under treatment for two and a half years. At her first visit the white blood cell count was 238,000. The globulin was 3.36 per cent, the albumin was 2.44 per cent and the fibrinogen was at the low normal level (286 mg. per hundred cubic centimeters). Roentgen treatment was started, and about one year after the patient's first visit the globulin was 2.38 per cent, the albumin was 4.40 per cent and the albumin-globulin quotient was 1.9. The fibrinogen had increased to 489 mg. per hundred cubic centimeters. During a period of leukopenia brought on by roentgen treatments, the albumin fraction and the fibrinogen decreased, while the globulin remained stationary.

The analyses in a case of pernicious anemia are given in case 2. The abnormally low globulin concentration found by Erben⁵ in this

5. Erben, F.: Die chemische Zusammensetzung des Blutes bei pernicioeser Anaemie, *Ztschr. f. klin. Med.* 40:266, 1900.

TABLE 6.—Miscellaneous Conditions

Case	Date	Sex	Per Cent Serum			Albumin- Globulin Volume, Cent	Mg. per 100 Cc. Plasma			Mg. per 100 Cc. Blood			Comment	
			Albu- min	Glob- ulin	Total Protein		Albumin- Globulin Quo- tient	Fibrino- gen	Choles- terol	Cal- cium	Fibrino- gen	Non- pro- tein Quo- tient		Nitro- gen Acid
1	3/ 1/26 2/11/27 5/21/27	F	2.44 4.40 3.40	3.36 2.38 2.45	5.80 6.75 5.85	0.7 1.9 1.4 33.2	283 450 283	119 230 110	11.6 9.6 8.7	11.7 4.9 8.6	30 31 24	4.6	Myelogenous leukemia; white blood cells, 238,000 Roentgen treatment since 3/26/26 Leukopenia; white blood cells, 650; no x-rays since April; died, spring, 1929
2	1/20/26	M	4.11	1.50	5.61	2.7	10.0	300	120	9.2	5.0	35	3.3	Pernicious anemia; blood sugar, 147 mg. per hundred cubic centimeters; chlorine as sodium chloride; plasma, 644 mg. per hundred cubic centimeters
3	2/ 1/26		5.60	0.50	5.90	20.0	10.5	109	135	8.4	5.2	36	5.2	Died week later; leteric index, 9; chlorine as sodium chlo- ride; plasma, 635 mg. per hundred cubic centimeters
	3/27/29	F	3.92	2.68	6.00	1.9	35.7	250	120	8.4	22	...	Pernicious anemia, very early stage, severe cystitis; leteric index, 22
	12/ 7/28	M	3.05	2.78	5.83	1.1	20.0	122	97	22.8	24	...	Chronic benzene poisoning, bleeding, leukopenia, anemia
	12/13/28		5.81	...	21.1	315	63	3.5	Transfused
4	1/10/29		4.03	2.03	6.06	2.0	26.8	330	135	8.8	6.1	Transfused
	1/22/29		3.13	2.10	5.23	1.5	26.3	291	125	9.8	7.2	
	2/ 1/29		3.79	2.39	6.18	1.6	333	115	7.2	Discharged January 31
	2/11/29		3.30	2.40	5.70	1.4	28.0	271	119	8.8	Feels well
5	4/ 1/29	M	3.05	1.30	4.35	2.3	33.7	254	90	5.1	Chronic benzene poisoning, slight; ambulant ease
6	2/14/26	F	3.77	3.65	7.42	1.0	17	...	Pemphigus (serum analysis)
7	2/14/26	F	4.10	3.73	7.83	1.1	Pemphigus (serum analysis)
8	9/21/27	F	2.98	3.21	6.22	0.9	40.8	520	172	10.4	6.2	33	2.0	Pemphigus
9	9/16/28	F	3.61	3.04	6.65	1.2	35.8	440	235	10.2	6.9	25	1.6	Xanthoma; diabetes mellitus; blood sugar 488 mg. per hundred cubic centimeters (not fasting)
10	11/12/23	M	4.30	3.30	7.60	1.3	46.2	570	156	11.4	5.8	Xanthoma; diabetes mellitus; blood sugar, 190 mg. per hundred cubic centimeters
	11/23/26		3.66	2.28	5.93	1.6	49.0	370	209	11.2	6.1	25	5.2	Insulin treatment; blood sugar, 210 mg. per hundred cubic centimeters
	12/30/26		4.13	2.49	6.62	1.7	41.3	550	204	4.5	One and a quarter hours after carbohydrate 68, protein 45, fat 68, blood sugar 236 mg. per hundred cubic centimeters
	1/18/27		5.05	2.87	7.92	1.8	48.0	500	139	3.7	...	3.7	Blood sugar, 178 mg. per hundred cubic centimeters

condition is present. In case 3, a case of early pernicious anemia, the globulin was 2.08 per cent. This relatively high concentration was due to a severe cystitis. The concurrent infection, however, did not affect the fibrinogen concentration, which was at the low normal limit. The icteric index was 22, and the urine gave a two plus urobilinogen reaction.

Cases 4 and 5 are of chronic benzol poisoning. The patient in case 4 on admission had an albumin-globulin quotient of 1.1. The globulin was increased and the fibrinogen markedly decreased, 122 mg. per hundred cubic centimeters. Tendency to bleeding and purpuric spots were present. With improvement in the clinical condition, the fibrinogen rose to 315 mg. per hundred cubic centimeters and maintained a high normal level from then on. Case 5 was a mild, ambulant case, in a man exposed to benzine fumes. The serum proteins were decreased, but the albumin-globulin quotient was normal.

These four cases resemble in the relationship between globulin and fibrinogen concentrations the cases of liver insufficiency shown in table 5. The next four cases in table 6 (6 to 10) resemble the infectious conditions in their protein concentrations.

Cases 6, 7 and 8, are cases of pemphigus. The albumin was moderately reduced and the globulin markedly increased. The fibrinogen was determined in one instance only and was found to be increased. The other two analyses were made on blood serum. The blister fluid was analyzed in case 6, and the protein concentrations practically checked the determinations made on the blood serum. The serum albumin was 3.77 per cent; in the blister fluid the albumin was 3.62 per cent. The serum globulin was 3.65 per cent; in the blister fluid the globulin was 3.73 per cent.

Nine and 10 are cases of xanthoma in diabetes mellitus. The globulin was increased, and the albumin was normal or slightly increased. The albumin-globulin quotient was decreased. The fibrinogen was increased. The patient in case 10 was put on insulin treatment. The albumin-globulin quotient improved, but the clinical condition remained unchanged.

Table 7 shows the analyses in four cases of acute nephritis and in eight cases of chronic glomerular nephritis.

In case 1, the blood picture during the recovery from a mild acute nephritis following measles in a man, aged 19, is shown. The first analysis gave an albumin-globulin quotient of 1.5, due to an increased globulin concentration (3.11 per cent). The fibrinogen was 308 mg. per hundred cubic centimeters. The urine showed numerous casts and

TABLE 7.—*Acute Nephritis and Chronic Glomerular Nephritis*

Case	Date	Sex	Per Cent Serum			Albu- min- Glob- ulin Quo- tient	Cell Vol- ume, per Cent	Mg. per 100 Cc. Plasma				Mg. per 100 Cc. Blood				Comment
			Albu- min	Glob- ulin	Total Pro- tein			Fi- brino- gen	Cho- les- terol	Cal- cium	Inor- ganic protein		Non- Nitro- gen	Uric Acid	Creat- inine	
											Phos- phorus	Phos- phorus				
1	9/10/26 12/20/26 7/ 6/27	M	4.54 4.06 4.70	3.11 2.14 2.22	7.65 6.20 6.92	1.5 1.9 2.1	47.3 44.0 42.0	308 195 214	249 173 151	9.5 10.6 ...	3.2 ... 3.6	37 29 31	... 4.2 3.2	...	Acute nephritis, mild, following measles Improved, less casts and red blood cells in urine No casts, no red blood cells in urine	
2	2/11/27	M	5.08	3.52	8.60	1.5	27.5	455	139	158	5.4	4.9	Acute nephritis; died ten days later	
3	3/ 1/26 3/ 8/26 3/15/26	F	2.37 1.56 1.65	2.06 2.12 4.25	4.43 3.68 5.90	1.2 0.7 0.4	36.4 36.2 30.5	563 406 511 16.1 18.3	126 240 187	3.5 5.1 4.2	3.0 4.6 3.6	Acute nephritis Died next day	
4	16/ 3/27	M	3.58	3.75	7.33	0.9	23.0	377	123	10.2	4.3	80	2.8	2.0	Acute nephritis; hematuria; died four weeks later	
5	4/ 4/26	F	3.41	2.40	5.81	1.5	37.8	350	...	9.4	...	47	Chronic glomerular nephritis; blood pressure, 220/130; coryza;	
6	2/ 4/27 7/27/27	F	3.07 2.57	2.49 2.17	5.56 4.91	1.2 1.2	34.7 26.6	532 422	357 178 3.5	47 53	3.6 6.7	3.0 ...	Chronic glomerular nephritis; infected tonsils; pyorrhea Albuminuria and casts 3 g.p.l.	
7	3/ 5/25 4/11/26	F	3.06 4.00	2.96 1.95	6.02 6.55	1.0 2.4	39.5 39.5	730 520	160 9.8	55 28	3.0	Chronic glomerular nephritis; blood pressure, 250/130; ur. alb. Phenolsulphonphthalein test 1 hour 40% excretion; blood pres- sure, 218/120	
8	3/ 9/27	M	3.89	2.26	6.15	1.7	...	466	134	9.9	...	36	Blood pressure, 210/125	
	7/10/27		3.53	2.18	5.71	1.6	31.8	612	...	10.2	4.3	40	2.5	...	Blood pressure, 210/120	
	4/29/29		3.48	2.20	5.68	1.6	37.8	582	122	4.4	44	2.9	...	Chronic glomerular nephritis; blood pressure, 165/110 Nausea and vomiting; blood pressure, 205/125
	1/13/26 5/26/26 8/18/26		3.13 4.71 3.15	1.22 1.54 2.50	4.35 6.25 5.65	2.6 3.1 1.3	39.2 37.8 30.6	294 414 373	...	9.9 9.8 8.9	... 4.6 5.2	47 61 94	3.1 6.1 3.6	2.3 2.2 4.1	Phenolsulphonphthalein test 1 hour 5% excretion; blood pres- sure, 210/145	
9	8/30/26 9/17/26	F	3.15 2.64	1.70 2.11	4.85 4.75	1.9 1.3	27.5 27.2	325 348	200 174	9.3 9.0	6.5 10.1	95 138	4.7 8.1	7.6 4.2	Feels improved; played golf; blood pressure, 185/128 Bed; blood pressure, 220/140; died 6 days later	
	5/17/27		2.90	1.25	4.15	2.3	36.8	518	415	8.8	...	59	15.0	3.6	Chronic glomerular nephritis; plasma chloride as sodium chlo- ride, 755 mg. per hundred cubic centimeters	
10	5/20/27		3.14	1.01	4.15	3.1	36.8	396	358	8.0	3.5	39	3.0	1.5	Plasma chloride as sodium chloride, 707 mg. per hundred cubic centimeters	
11	5/16/27 6/ 8/27	F	2.76 2.38	1.58 1.60	4.35 3.98	1.7 1.5	25.2 24.5	300 435	400 294	9.1 9.6	5.4 5.4	35 36	3.8	Chronic glomerular nephritis	
12	10/20/27	F	4.55	1.10	5.65	4.0	82.6	256	306	10.4	5.9	62	6.0	3.8	Chronic glomerular nephritis	
13	1/12/27 10/10/27	M M	3.95 4.25	1.80 1.50	5.75 5.55	2.2 3.3	18.8 26.6	578 333	...	10.0 8.3	...	167 30	4.9 5.0	9.1 ...	Chronic glomerular nephritis; died 14 days later Chronic glomerular nephritis; died three months later	

a one plus albumin reaction. Three months later the globulin had decreased to 2.14 per cent, the fibrinogen was 195 mg. per hundred cubic centimeters and the quotient was 1.9. Seven months after this analysis there was a further increase in the quotient, due to a rise in the albumin fraction; the fibrinogen was 214 mg. per hundred cubic centimeters. The urine showed no casts and only a faint trace of albumin.

The patient in case 2 came to the clinic with acute nephritis and died ten days later. The quotient was 1.5 with a normal albumin concentration and a globulin concentration increased to 3.52 per cent. There was considerable retention of nitrogen.

The patient in case 3, a girl aged 16, died within fifteen days. The globulin rose from a concentration of 2.06 to 4.25 per cent the day before death. Coincident with this increase there was a decrease in the albumin fraction from 2.37 to 1.65 per cent on the last analysis. The fibrinogen was markedly increased.

Patient 4 had a subacute nephritis with pronounced hematuria. He died about four weeks after the date of the reported analysis. The albumin-globulin quotient was 0.9, mainly due to the increased globulin concentration of 3.75 per cent. There was moderate azotemia.

In cases 5 and 6 the patients had chronic glomerular nephritis with mild infections. The patient in case 5 (coryza with elevation of temperature at the time of analysis) showed a quotient of 1.5, and the patient in case 6 (infected tonsils and pyorrhea) had an albumin-globulin quotient of 1.2 on two occasions. Case 7 (chronic glomerular nephritis) has been followed since 1923. The slightly increased globulin and the invariably high fibrinogen lead one to suspect a focus of infection in this case.

Case 8 was followed for three years, and the analyses during the last year of life are shown. On only one occasion was the globulin found to be increased (2.50 per cent), and six days before death its concentration was 2.11 per cent. The albumin-globulin quotient fell from 2.6 to 1.3, but the reduction in the quotient is due to the decrease in the albumin fraction. The fibrinogen was slightly increased.

Cases 9 to 12 are ambulant cases of chronic glomerular nephritis. None of these cases showed an increased globulin concentration. The patient in case 12 (globulin 1.80 per cent) came to the clinic with a severe retention of nitrogen (nonprotein nitrogen 167 mg. per hundred cubic centimeters, creatinine 9.1 mg. per hundred cubic centimeters). He died within a week.

In glomerular nephritis, uncomplicated by an infection, the serum proteins do not vary considerably from the normal. There is a tendency to a decreased albumin concentration, and this becomes more pronounced in the later stages. The fibrinogen may be normal or slightly increased.

Table 8 gives the plasma proteins in five cases of nephrosis. Case 1 has been followed since 1923. The globulin occasionally rise above the normal, but only slightly. A mild respiratory infection was present at the time. The albumin was materially decreased. The average serum protein concentrations (fifteen analyses) were: albumin, 2.08 per cent; globulin, 2.01 per cent. The fibrinogen and cholesterol were much increased in concentration. With improvement in the clinical condition the albumin increased in concentration, and the albumin-globulin quotient rose.

Case 2 presents a similar picture. The albumin was much decreased and the globulin was normal or only slightly increased. The average concentrations (seven analyses) were: albumin, 2.10 per cent; globulin, 2.30 per cent.

Case 3 also had a much reduced albumin concentration (1.57 per cent) which gradually increased to 2.47 per cent. The average concentrations of the six analyses in this case were: albumin, 2.36 per cent; globulin, 1.75 per cent.

The low albumin-globulin quotient in cases 4 and 5 is also attributable to the low albumin concentration. Case 6, an ambulant clinic case, showed the unusual phenomenon of decreased albumin concentration with a correspondingly decreased globulin concentration. The patient in this case, unfortunately, was lost sight of after two examinations, but the averages of these two closely corresponding determinations were: albumin, 2.36 per cent; globulin, 0.54 per cent; albumin-globulin quotient 4.3. The fibrinogen concentration was normal. The cholesterol was much increased.

None of these patients showed any retention of nitrogen. All had intense albuminuria, casts and renal epithelial cells in the urine, edema and low basal rate. The calcium concentrations were always below normal, the cholesterol was invariably much increased and the fibrinogen concentrations, with the exception of that in case 6, were much increased. Improvement in the clinical condition reflected itself in an increase in the albumin concentration. Coincident with this increase in the albumin concentration there may be a slight decrease in the globulin and fibrinogen concentrations.

COMMENT

Assuming the serum proteins to be formed outside the circulation, one may consider the liver, and the intestinal mucosa as well as the blood-forming organs as the most likely sites of formation. The entrance of the proteins into the blood stream will be governed by the state of endothelial permeability in these organs. It is known that the normal endothelium, with the exception of the capillaries in the liver, in the intestinal mucosa and possibly the lungs is impermeable to the plasma

TABLE 8.—*Nephrosis*

Case	Date	Sex	Per Cent Serum		Albu- min- Glob- ulin Quo- tient	Cell Vol- ume, Cent	Mg. per 100 Cc. Plasma			Per Cent Blood		Comment		
			Albu- min	Glob- ulin			Total Pro- tein	Chlo- rides as NaCl	Oho- les- terol	Cal- cium	Non- protein Nitro- gen Acid			
1	12/ 5/23	M	1.03	2.72	3.80	0.4	38.5	661	564	443	8.4	30.0	..	Urine albumin; 6.8 g.p.l., few f. gr. and hyal. casts; R.B.C. and renal cells; P.S.P. test (12/5/23) 1 hr. intraven. 40% excretion
	1/ 4/24		1.46	1.34	2.80	1.1	33.0	1,000	594	425	8.7	35.0	2.5	Basal rate, ~33%; blood pressure, 150/90
	2/ 8/24		1.93	1.73	3.66	1.1	40.0	770	...	395	8.5	
	3/ 7/24		1.78	2.30	4.08	0.8	40.5	535	640	445	8.0	
	6/ 5/24		2.34	2.16	4.50	1.1	39.0	625	607	...	8.3	40.0	4.7	
	9/25/24		1.98	1.86	3.84	1.1	43.0	650	...	225	8.2	37.0	3.4	
	1/ 8/25		2.18	2.12	4.30	1.0	40.1	650	625	278	7.6	41.0	2.0	
	4/30/25		2.22	1.54	3.76	1.4	42.3	606	640	...	7.1	31.0	3.7	
	7/27/25		1.55	2.21	3.76	0.7	39.8	605	585	357	8.4	31.0	4.8	
	9/17/25		1.90	2.95	4.85	0.7	41.7	755	610	238	7.3	32.0	4.2	
	2/ 5/26		2.16	1.68	3.84	1.3	42.8	735	585	455	7.6	40.0	...	
	7/21/26		3.13	2.75	5.88	1.1	45.0	745	...	360	9.9	35.0	2.8	Basal rate, ~8%; blood prssure, 135/80; improved, feels well
12/ 8/27		3.08	1.74	4.82	1.8	45.5	395	625	250	9.5	32.0	...	Greatly improved clinically	
2/23/28		2.56	1.17	3.73	2.2	41.4	340	595	210	8.5	29.0	2.9		
2	6/12/24	M	2.07	2.50	4.57	0.8	41.7	667	552	666	8.5	35.0	1.5	Urine albumin, 7 g.p.l., many casts, few red blood cells and renal cells
	7/ 8/24		2.08	2.83	4.91	0.7	37.6	700	...	476	8.0	40.0	3.2	Blood pressure, 98/70; basal metabolic rate, ~34%; 1 hour P.S.P. test intraven. 56% excretion
	7/17/24		2.27	2.63	4.90	0.9	39.0	750	...	418	8.7	38.0	3.3	
	9/11/24		2.16	1.93	4.09	1.2	42.5	550	654	563	8.2	36.0	3.0	
	10/ 2/24		1.87	2.04	3.91	0.9	42.0	520	681	417	8.1	30.0	...	
	11/ 5/24		2.16	2.14	4.30	1.0	40.3	580	583	447	7.8	30.0	...	
	11/18/24		2.12	2.08	4.20	1.0	40.0	745	566	...	7.9	30.0	...	Decrease in casts; basal rate~8%
	3/ 10/ 6/26	M	1.57	1.92	3.49	0.8	36.5	642	627	560	8.0	30.0	...	Urine albumin 6 g.p.l., many casts, blood pressure, 100/70; basal rate, ~8%
	10/25/29		1.82	1.79	3.61	1.0	36.5	1,070	617	446	9.0	24.0	2.8	Pyorrhea of lower gums; edema
	1/18/27		2.61	1.55	4.16	1.7	32.0	580	606	460	9.3	32.0	...	
	5/10/27		2.88	1.42	4.30	2.0	38.0	566	642	352	9.2	32.0	2.2	
	6/28/27		2.69	1.91	4.60	1.4	36.0	495	620	357	9.7	39.0	2.2	Improved; number of casts reduced; feels well; no edema
9/12/27		2.47	1.83	4.30	1.4	39.0	650	612	283	...	32.0	...		
4	9/22/27	F	0.97	1.55	2.52	0.6	26.9	580	560	760	7.2	44.0	...	
	3/ 1/26	F	1.63	2.30	3.93	0.7	36.0	450	29.0	3.2	Intense albuminuria, many casts, edema, headaches
5	3/15/26		2.47	1.58	4.05	1.6	37.2	480	635	333	8.6	29.0	2.5	
	5/11/26		2.33	2.35	4.68	1.0	...	483	620	333	8.5	29.0	...	
6	12/23/25	M	2.38	0.50	2.88	4.7	...	236	...	242	9.0	33.0	3.1	Albuminuria, 5 g.p.l., many granular and fatty casts
	12/31/25		2.35	0.59	2.94	4.0	48.5	...	600	202	9.1	30.0	...	
7	3/ 3/24	F	0.83	2.01	2.84	0.4	33.0	1,020	524	148	8.3	24.0	1.5	Intense albuminuria; intercurrent fatal pneumonia
			0.78	2.16	2.94	0.4	37.5	1,530	

Urine albumin; 6.8 g.p.l., few f. gr. and hyal. casts; R.B.C. and renal cells; P.S.P. test (12/5/23) 1 hr. intraven. 40% excretion

Basal rate, ~33%; blood pressure, 150/90

Basal rate, ~8%; blood pressure, 135/80; improved, feels well
Greatly improved clinically

Urine albumin, 7 g.p.l., many casts, few red blood cells and renal cells
Blood pressure, 98/70; basal metabolic rate, ~34%; 1 hour P.S.P. test intraven. 56% excretion

Decrease in casts; basal rate~8%

Urine albumin 6 g.p.l., many casts, blood pressure, 100/70; basal rate, ~8%
Pyorrhea of lower gums; edema

Improved; number of casts reduced; feels well; no edema

Intense albuminuria, many casts, edema, headaches

Albuminuria, 5 g.p.l., many granular and fatty casts

Intense albuminuria; intercurrent fatal pneumonia

proteins.⁶ The capillaries of the bone-marrow, the spleen and the blood-forming organs as a whole are permeable to the formed elements of the blood and may be assumed to be permeable to the plasma proteins. The greatest known endothelial permeability is in the liver. The lymph from the liver approximates the plasma in its protein concentration. The lymph secreted by the intestinal mucosa contains only about two thirds of the plasma protein concentration, and it is assumed that only the smaller molecules pass out.⁷ If the serum proteins enter and escape the circulation as entities, and are only partly or not at all broken down while in the circulation, their relative concentration will depend also to a certain degree on the state of capillary permeability in other parts of the organism. Petersen, reasoning on the basis of anatomic structure and obvious function, made the assumption that the capillary endothelium has become specialized in the control of permeability. "If the endothelial wall of the capillaries acts in the manner of an ultra filter, allowing water, crystalloids and in some cases colloids to pass through, then any change in this ultra filter will be accompanied by a change in the relative concentrations of the colloids of different viscosities which it allows to pass through."⁸ Heightened permeability of the capillaries may be brought about by any of the factors which cause increased permeability of the cell, by dilatation due to physical, nervous or chemical stimuli,⁹ by increased capillary pressure or by injury.¹⁰

The proteins of the plasma which may be isolated by chemical methods are, in the descending order of their viscosities, fibrinogen, euglobulin, pseudoglobulin and albumin. The greater viscosity of the globulin fraction is mainly due to the euglobulin which constitutes approximately 46 per cent of the fraction and has a viscosity of 1.21 for a 1 per cent aqueous solution. The viscosity of a 1 per cent pseudoglobulin solution is 1.12, and the viscosity of the globulin fraction in like concentration is 1.16. The viscosity of a 1 per cent albumin solution is 1.08. The viscosity of water is taken as 1 in these measurements.

The viscosities of the serum proteins parallel their "molecular weight" as determined by the centrifugal method. Svedberg¹¹ obtained

6. Krogh, A.: *Anatomy and Physiology of the Capillaries*, New Haven, Conn., Yale University Press, 1924, p. 230.

7. Krogh (footnote 6, p. 231).

8. Petersen, W. F.; Levinson, S. A., and Hughes, T. P.: *Studies in Endothelial Permeability; Effect of Epinephrin on Endothelial Permeability*, *J. Immunol.* **8**:323, 1923.

9. Krogh (footnote 6, p. 323).

10. Landis, E. M.: *Micro-Injection Studies of Capillary Permeability*, *Am. J. Physiol.* **81**:124, 1927.

11. Svedberg, T., and Fahrseus, R.: *A New Method for the Determination of the Molecular Weight of the Proteins*, *J. Am. Chem. Soc.* **48**:430, 1926. Svedberg, T., and Sjogren, B.: *The Molecular Weights of Serum Albumin and Serum Globulin*, *J. A. Chem. Soc.* **50**:3318, 1928.

by this method the value of 67,500 for serum albumin and 103,800 for serum globulin. Svedberg considered these fractions as entities and questioned the existence of euglobulin and pseudoglobulin preformed in the serum.¹² Sørensen, on the other hand, considered that the formula $E_n P_m$ when n and m are variables, expresses the composition of the serum globulin fraction. He considered euglobulin an addition product of pseudoglobulin and a lipid.¹³ The mechanism of the rise of the globulin fraction in infections and toxemias is not explained. This may possibly be a defensive mechanism to combat the infection or result from the changed conditions due to the infection itself. Many investigators attribute the significance of the globulins in infections to the addition-combination with a lipid. Troensgaard and Koendahl¹⁴ stated that a cholesterol-globulin complex is the important factor. One may assume that the greater viscosity of the euglobulin fraction as compared to the pseudoglobulin is due to an addition or combination of the pseudoglobulin with a lipid-like substance.

To the view that the serum proteins are formed outside the circulatory system and that the relative impermeability of the capillary endothelium as a whole prevents the escape of the serum proteins, the difference in size and viscosity between the two fractions is of importance. The partial or complete permeability of the capillaries in certain organs and the changes in capillary permeability in disease are also relevant. A shift in the relative concentrations of the fractions, due to a relative and absolute increase in the globulin fraction, may from this point of view indicate greater permeability in the organs which are the main sources of the serum proteins as well as increased production or decreased destruction of that fraction. It may also indicate a decrease in euglobulin formation with a consequently greater influx of the less viscous part, the pseudoglobulin. On the other hand, a shift in the albumin-globulin quotient due to an absolute decrease in the albumin fraction may denote increased permeability in the capillaries normally impermeable to the serum proteins, as well as lessened production or increased destruction of the smaller molecule. The greater protein concentration and the relatively greater globulin concentration of inflammatory exudates as compared to transudates, illustrate the effect of increased permeability as it is present in inflammations. Robertson considered an altered permeability of the tissue cells in infections as the possible cause

12. Editorial, J. A. M. A. **92**:233 (Jan. 19) 1929.

13. Sørensen, S. P. L.: On the Solubility of the Serum Globulins, *Comptes rendus des travaux du laboratoire de Carlsberg* **15**:14, 1925.

14. Troensgaard, N., and Koendahl, B.: Cholesterian als prostetische Gruppe im Serum Globulin, *Ztschr. f. physiol. Chem.* **153**:111, 1926.

of the change in the albumin-globulin quotient.¹⁵ Prolonged ether or chloroform anesthesia, with its known effect on cellular permeability has been shown to cause a decrease in the albumin-globulin quotient owing to a decrease in the albumin fraction and an increase in the globulin fraction.

✓ The changes found in the relative concentrations of serum proteins and fibrinogen in infectious conditions point to increased permeability. The fibrinogen is increased, the albumin is decreased slightly in the milder infections which do not affect the globulin concentrations and decidedly in the more severe and fatal infections. In the more severe infections the globulin is increased. In fatal infections the globulin is materially increased, and the increase parallels the progress of the condition.

The changes found in certain liver and gallbladder conditions differ from those encountered in the more severe generalized and localized infections. In cirrhosis of the liver there is a gradual, relatively mild decrease in the albumin fraction and a moderate rise in the globulin concentration. The fibrinogen may be slightly increased at the onset, but decreases to a low normal level and below that as the condition progresses. Concurrent infections cause only a slight increase in the fibrinogen concentration, while the response in the serum proteins is exaggerated, even in mild infections. This relationship, increased globulin concentration with a normal or even subnormal fibrinogen concentration, was not found in any of the infections studied, except when there was evidence of liver insufficiency. It was present in the case of myelogenous leukemia and in the case of benzene poisoning, conditions in which the bone-marrow is known to be affected. Is the moderate rise in the globulin in these cases due to an increased release from the bone-marrow? Petersen noted that during portal blockade the fibrinogen in the lymph is reduced, while the relation between albumin and globulin remains unaltered. He stated that "assuming the fibrinogen comes from the liver this reduction can be explained by assuming that the fluid coming through comes from parts of the splanchnic area other than the liver. As soon as the blockade results in capillary injury there is increase in the fibrinogen, globulin, sugar and bile pigment."¹⁶ Howe¹ considered it most likely that other tissues aside from the liver are concerned in the production of the serum proteins and that the mechanism of the formation of fibrinogen differs from that of the globulins. If the liver is the

15. Robertson, T. B.: *Principles of Biochemistry*, Philadelphia, Lea & Febiger, 1924, p. 38.

16. Petersen, W. F.; Jaffe, R. H.; Levinson, S. A., and Hughes, T. P.: *Studies in Endothelial Permeability III. The Modification of the Thoracic Lymph Following Portal Blockade*, *J. Immunol.* 8:361, 1923.

main source of the fibrinogen while the serum proteins are derived from other sources as well, e. g., the blood-forming organs and the intestinal mucosa, it is understandable that in a condition in which the liver becomes less permeable the fibrinogen concentration in the blood becomes reduced, while the globulin concentration remains unaltered or is increased and the albumin concentration is reduced. Decreased fibrinogen concentrations have been demonstrated in extensive injury to the liver. Decreased fibrinogen concentrations in cirrhosis of the liver is mentioned by Pickering.¹⁷ Fibrinogen is extremely variable in its concentrations; the range of the physiologic concentrations is wide. It is found slightly increased during the menstrual period, increased during the later months of pregnancy and during puerperium. It is increased in even slight infections, after exposure to x-rays, small doses of liver poisons and in all suppurative and inflammatory processes. Any irritation of the liver seems to call forth an increased fibrinogen concentration in the blood plasma. If this increase does not take place, although the clinical blood picture as a whole point to a condition which ordinarily would result in irritation of the liver and increased fibrinogen concentration, one may conclude that the liver function is impaired. Such a change in the relative concentrations is well expressed by the globulin-fibrinogen quotient.

The average physiologic globulin-fibrinogen quotient is 6.8 for males and 6.2 for females. In the cases of localized and generalized infections shown in table 4, it is generally below the average normal. It ranges between 2.2 and 11.6 and the average of all the cases is 5. It is increased and above the normal in the cases of severe and fatal infections, due to the great increase in the globulin concentrations. It was also found to be slightly increased in two cases of syphilis in which the patients had not been treated and in a case of arrested pulmonary tuberculosis in which the icteric index was 12. However, even though increased in these cases, the increase is slight when compared to the quotients found in the cases of hepatic cirrhosis. In these cases the quotient ranges between 6.5 and 24.7, and the average of the cases reported is 11.5. As the condition progresses, the quotient increases; it is an index of the severity of the condition. The increase in the globulin-fibrinogen quotient in these cases is due to the relatively low fibrinogen concentrations, while in the fatal infections it is mainly due to the material increase in the globulin concentration.

In jaundice without elevation in temperature there is likewise a temporary increase in the globulin fraction with or without a simultaneous decrease in the albumin fraction. There is practically no varia-

17. Pickering, J. W.: *The Blood Plasma in Health and in Disease*, London, W. Heinemann, 1928, p. 24.

tion in the fibrinogen concentration. In cholecystitis and in jaundice due to the use of arsphenamine increase in fibrinogen concentration is present, and the albumin-globulin quotient is reduced, owing to an increase in the globulin concentration and a decrease in the albumin concentration. The blood picture in the latter conditions is similar to that of other infections, but the rise in the globulin is more marked and the rise in the fibrinogen less so.

In chronic glomerular nephritis the total serum protein concentration is somewhat reduced with a normal or slightly reduced globulin. The main reduction takes place in the albumin fraction. The fibrinogen is often found to be increased. In acute nephritis there is an increase in the globulin fraction, an increase in the fibrinogen and the albumin is decreased. The changes in the proteins in acute nephritis are similar to the concentration changes found in infectious conditions.

The marked decrease in the albumin fraction is a familiar picture in nephrosis. The abnormally low albumin-globulin quotient in these cases is entirely due to this decrease. The blood picture on the whole is one of increased permeability. The calcium concentration is reduced below the normal and the cholesterol and fibrinogen concentrations are much increased, especially if edema is present.

One of the functions of the plasma proteins is the maintenance of equilibrium between the hydrostatic (filtration) pressure of the blood and the difference in osmotic pressure between the blood and tissue fluids. The capillaries are permeable to crystalloids, and normally any difference in these constituents is equilibrated. The protein content of the blood, however, is higher than that of the tissue lymph, and it is this difference in osmotic pressure which counterbalances the hydrostatic pressure which filters off the water. The effective osmotic pressure of the human serum is approximately 40 cc. of water column. It is mainly due to the albumin concentration, which contributes 7.54 cm. of column per gram of albumin in 100 cc. of serum against 1.95 cm. of column for every gram of globulin in 100 cc. of serum.¹⁸ A low albumin concentration will therefore affect the osmotic pressure of the blood far more than a lowered globulin concentration. The edema of nephrosis is a filtration edema due to a lowered colloid osmotic pressure.¹⁹ The red corpuscles by imbibition of water, thereby diminishing the water content of the plasma, may also take part in the regulation of the osmotic

18. Govaerts, Paul: La formation des oedemes, *Bull. d. l'acad. roy. de méd. de Belg.* **7**:356, 1927.

19. Iversen, P., and Nakazawa, F.: Ueber die Biochemie des Filtrationsoedem, *Biochem. Ztschr.* **191**:307, 1927.

pressure.²⁰ The corpuscular volume in filtration edema is often higher than could be expected from a determination of the red blood cell count.

The picture obtained in cases of nephrosis is in certain respects the opposite of that obtained in the diseases of the liver and gallbladder. The total serum protein concentration is much reduced, and the reduction is in the smaller molecule, i. e., the albumin fraction. The cholesterol and fibrinogen are much increased. If in the hepatic cases and in the infectious conditions one considers the rise in the globulin concentrations as due to a greater permeability in the organs which are sources of the serum proteins, one may consider the low albumin concentration in nephrosis as due, or partly due, to a heightened permeability of the capillaries normally not permeable to the serum proteins. Likewise the moderate decrease in the albumin concentrations in infections and the hepatic cirrhosis may be ascribed to increased peripheral capillary permeability. The increase in fibrinogen as well as cholesterol in nephrosis can be ascribed to a greater release of these substances on account of a general increased cellular permeability.

SUMMARY

The two fractions of the serum protein, the albumin and globulin and the plasma fibrinogen together with other blood constituents significant of the clinical condition have been determined in diabetes mellitus, benign glycosuria, localized and generalized infections, diseases of the liver and the gallbladder and in renal conditions.

The methods used and the physiologic concentrations determined by these methods are stated.

The plasma proteins are within the physiologic limits in diabetes mellitus and in benign glycosuria.

In infections the albumin is decreased, slightly in mild cases and decidedly in the more severe infections. The fibrinogen is increased, even in slight infections which do not call forth an increased globulin concentration. In the more severe infections the globulin is increased, and the increase parallels the severity of the condition.

In cirrhosis of the liver the albumin is decreased and the globulin is increased. The changes in the serum protein concentrations, however, are not so marked as in the infectious conditions. The fibrinogen is a low normal or decreased. In jaundice without elevation of temperature, the serum proteins are normal or increased, the albumin is generally within the normal limits and the globulin is increased. The fibrinogen remains within the normal limits. In cholecystitis and in jaundice due to the use of arsphenamine the picture is similar to that found in infections.

20. Schade, H.: *Die physikalische Chemie in der inneren Medezine*, ed. 3, Leipzig, Theodore Steinkopff, 1923, p. 178.

In chronic, glomerular nephritis, in the absence of an infection, the serum proteins are slightly reduced, especially the albumin fraction. The fibrinogen is often slightly increased. In acute nephritis the changes found are the same as in infections. In nephrosis the albumin is materially decreased, the globulin is normal and the fibrinogen is much increased.

The significance of the changes in the protein concentrations and their bearing on questions of site of formation, port of entry and functions are discussed. The importance of complete chemical analytic studies and the recognition of complications which may mask the results expected from the pathologic condition studied are evidenced. The difference in relationship of globulin to fibrinogen in infections and disturbed hepatic function is pointed out. The diagnostic and prognostic value of changes in the albumin-globulin quotient and in the globulin-fibrinogen quotient is discussed.

POSTOPERATIVE RESULTS IN TOXIC GOITER *

NORMAN E. CLARKE, M.D.

AND

IRENE BLACK

DETROIT

Since Moebius ¹ in 1886 focused attention on the causative association of the thyroid with the disease which is now called hyperthyroidism, surgical intervention has become the almost universal therapeutic agent for relief from this condition. During the past fifty years the number of operative cases has increased enormously, yet there are surprisingly few accurate follow-up studies for determining what results thyroidectomy has produced on these patients. There is wide variation in the successful operative results reported in the relatively few postoperative studies. In a group of thyroidectomies reviewed one year later at the Lahey Clinic,² it was claimed that cure was obtained in 92 per cent. In a series of cases which includes both exophthalmic and toxic adenoma, reported by Judd,³ it was stated that 65 per cent of the patients having severe hyperthyroidism were cured, while 80 per cent who had toxic adenoma were relieved from their toxic symptoms and cured. Among the German surgeons ⁴ there have been reports of cure in 30 per cent of cases of hyperthyroidism following thyroidectomy, while Bram ⁵ expressed the belief that a fair estimate is 18 per cent for those patients who remained cured by thyroidectomy after a lapse of several years. With the exception of the report made by Lahey, most of the other investigators have depended on mailed questionnaires for their information.

In our own report we have set up definite criteria for the judging of post-thyroidectomy results, these being (*a*) personal examination and questioning of the patient, (*b*) obtaining of the patient's basal metabolic rate, (*c*) the avoidance of pointed direct questions, eliciting informa-

* Submitted for publication, Nov. 22, 1929.

* From the Cardiac Service, Grace Hospital.

1. Moebius, P. J.: Vom Verhältnisse der Polioencephalitis zur Basedow-schen Krankheit en Jendrassik, in Schmidt, E.: Jahrb. d. Med. **210**:237, 1886.

2. Smith, L. W.; Clute, H. M., and Strieder, J. W.: Surg. Gynec. Obst. **46**:325 (March) 1928.

3. Judd, E. S.: Results of Operation for Adenoma with Hyperthyroidism and Exophthalmic Goiter, Ann. Surg. **72**:145, 1920.

4. Quoted by Bram (footnote 5).

5. Bram, Israel: Goiter; Nonsurgical Types and Treatment, New York, The Macmillan Company, 1924.

tion without the use of suggestion and (d) the collection and correlation of the data by one other than the surgeon. The present lack of careful follow-up studies of the end-results of thyroidectomy by personal questioning and examination of patients a few years after operation is worthy of consideration in view of the sureness with which the surgeons have attacked this problem.

Common experience shows the striking immediate effect of surgical intervention for hyperthyroidism in most instances, but the condition of patients months or years after operation has been performed alone furnishes the true facts on which we may evaluate the real benefits of thyroidectomy. Many features other than the surgical removal of thyroid tissue may be factors in the immediate improvement. The hospital and the surgical experience have a powerful psychotherapeutic value; the rest before and after the operation have proved to be of great benefit, while the reaction with elevation in temperature, resorption of hemolyzed blood and the traumatic changes to the gland may be of unknown value.

The present study of the end-results of thyroidectomy consists of two parts. In the first part we have summarized the pertinent observations on the condition of 181 patients admitted to Grace Hospital during 1927 with a diagnosis of toxic goiter, who were later operated on. In the second part we have summarized similar pertinent observations on many of the same patients after an average time of two and one-half years had elapsed following the operation. We felt that any beneficial results obtained through thyroidectomy would have been consummated within two and one-half years and likewise that most untoward results would be present within the same time. In order to secure as great accuracy as possible, letters were written to this group of patients asking them to return. All those who did were examined and their interval history obtained, obviating the dangers and inaccuracies of mailed questionnaires. A basal metabolism test was also performed on practically all patients who presented themselves for this study.

INCIDENCE AND SYMPTOMS

Distribution According to Sex and Age.—Of the 181 patients whose records were reviewed, 34 were males and 147 females. The age grouping of the males showed 8 in the third decade, 11 in the fourth decade, 7 in the fifth decade and 8 in the sixth decade of life. The females showed 8 in the second decade, 46 in the third decade, 44 in the fourth decade, 25 in the fifth decade, 22 in the sixth decade and 2 in the seventh decade of life. The disproportion between the males and females, a little better than 4.3 females to 1 male, conforms to the usual experience, others reporting even higher ratios. The difference in age grouping is important, for while the males show a fairly equal distribu-

tion in the decades from 20 to 60 years of age, the greatest incidence among the females is between the ages of 20 and 50 years, or the period of active sexual life or child-bearing. This relationship of sex with the disease is somewhat substantiated, as we show in a later table, by the observed frequency of symptoms of toxic goiter occurring coincident with pregnancy.

Duration of Symptoms.—The duration of the symptoms, or the period which elapsed between the time when the disease was first observed until operation, was not stated in 23 records. Of the 158 patients who were able to give a definite time for the onset of the symp-

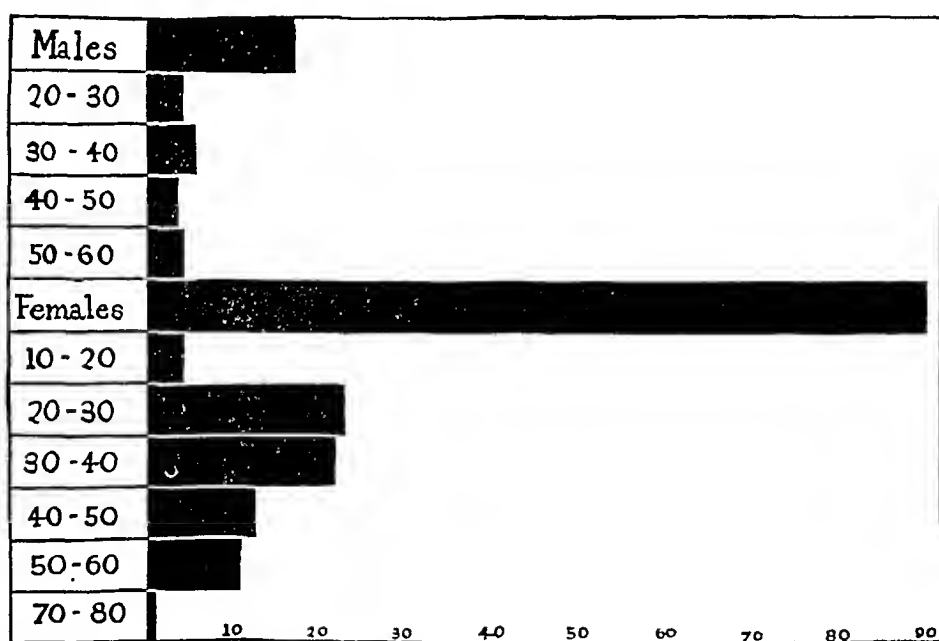


Chart 1.—Chart showing distribution according to sex in toxic goiter, the ratio being 4.3 females to 1 male. The numbers at the bottom of each chart indicate the number of patients.

toms, 2 had noticed the symptoms for less than one month. Among the others, there were 15 whose symptoms had been present from one to three months, 27 from three to six months, 11 from six to nine months and 37 from nine to twelve months. In 22 patients the symptoms were present from one to two years, in 18 from two to four years, in 10 from four to six years, in 8 from six to ten years and in 8 over ten years. Over one half of the total number of patients had had symptoms one year or less, but a surprisingly large number, or practically one-half, had had symptoms at least one year and a little more than 16 per cent claimed to have had symptoms for four years or longer.

Incidence of Various Symptoms.—In listing the symptoms complained of by the 181 patients, we observed great variation, but also a few symptoms which were common to almost all. The most frequent symptom complained of was nervousness. This was described by many as a feeling of inward tension or trembling, not one of actual shaking or movement. The next symptom most commonly complained of was palpitation, described by some as heart consciousness associated with a very rapid heart rate, while others described it as periods of marked heart consciousness induced by exertion or emotional excitement. The third most commonly complained of symptom was dyspnea, either as shortness of the breath on lying down, as shortening of the breath on exertion or excitement or like a feeling of choking such as that induced

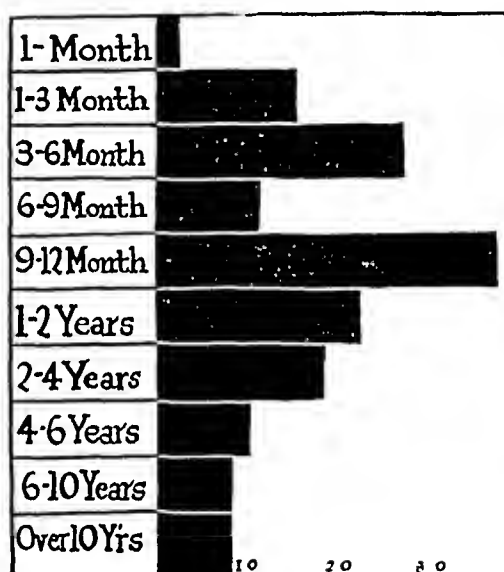


Chart 2.—A graphic presentation of the duration of symptoms in toxic goiter, time being reckoned from when symptoms were first noticed until operation.

by tracheal constriction. About one third of the patients had noticed an enlargement of their neck and a little more than one-third complained of weakness. A rather frequent complaint was irritability, while only 15 per cent had observed increased prominence of their eyes or exophthalmos. In 21 of the 181 patients, we were able to elicit a definite mental or emotional shock preceding the onset of the symptoms of toxic goiter. There were gastro-intestinal symptoms in 60 patients, most patients having two or more complaints such as diarrhea, flatulence, nausea or vomiting. The following list shows the incidence of the various symptoms in order of frequency: nervousness 156, palpitation 138, dyspnea 94, weakness 65, enlarged neck 58, perspiring 49, nausea 40, irritability 37, choking 32, vomiting 27, diarrhea 24, dizziness 23, edema of legs 23, pressure, cough, etc. 22, mental strain, emotional 21, hot

flashes 16, heart pain 15, exophthalmos 15, abdominal pain 11, abdominal distress 10, flatulence 9 and constipation 4.

The Use of Iodine.—Thirteen of the 181 patients gave a history of having used iodine salt for some time previous to the onset of their symptoms. A compound solution of iodine was given to 101 of these patients previous to their operation, while in 42, iodine was continued after operation. Apparently no distinction was made between those cases diagnosed as toxic adenoma or exophthalmic goiter in the administration of iodine, and no untoward results were mentioned with any patient, the patients with toxic adenoma apparently benefiting equally with those whose condition was diagnosed as exophthalmic goiter.

Changes in the Weight of Patients with Hyperthyroidism.—In 58 of the 181 patients no mention was made of weight or its change or lack of change with the onset of the disease. Of the 123 patients concerning whom information was available, a loss of weight had occurred in

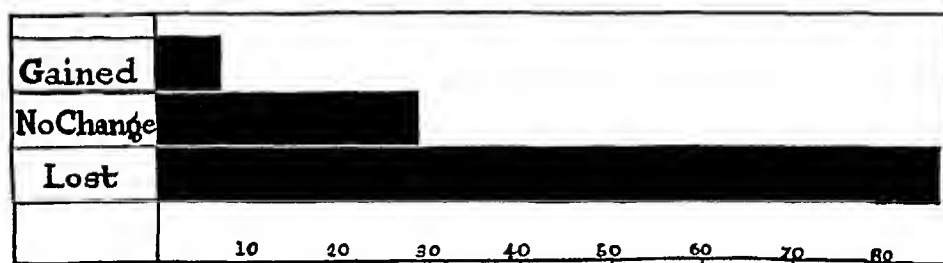


Chart 3.—The weights in 123 patients with toxic goiter showing 70 per cent losing weight while 30 per cent gained or showed no change.

87, or 70 per cent. There had been a gain of weight in 7 or 6 per cent, while the weight did not change in 29, or 24 per cent. There were, therefore, 36 patients, or 30 per cent of the entire group, in whom the disease caused no change or even allowed a gain in weight, but the great majority, 87 or 70 per cent, lost weight with the onset of hyperthyroidism.

Basal Metabolism Records.—A basal metabolism was performed on only 62 of the 181 patients previous to operation. Of these, 8, or almost 13 per cent, showed a basal metabolic reading between -10 and $+10$, 11 each showed readings between $+11$ to $+20$ and $+21$ to $+30$. There were 10 patients who had basal metabolic readings between $+30$ and $+40$, while 9 were between $+40$ and $+50$ and 4 each were between $+50$ to $+60$ and $+70$ to $+80$. There were 2 between $+80$ and $+90$, while 3 showed basal metabolic rates above $+90$. In those cases in which more than one basal metabolic rate was taken, marked variations were observed. In 1, an initial reading was $+60$ while a

second reading was +18. Another showed an initial rate of +62 with a second reading of +15. Another showed an initial rate of +42 and a later reading of -6, while others showed less but still marked variations. The ordinary basal metabolic test done in general hospitals and practice may lead to very erroneous conclusions unless rechecked and the result carefully compared with the pulse rate and general clinical observations.

Blood Pressure Records.—There were 60 patients' records which showed no blood pressure readings. Of the 121 cases in which blood pressure records were available, we have obtained the average systolic, diastolic and pulse pressure with a further classification of each division into the average mean and extreme readings. The average systolic reading for the entire 121 patients was 133 mm. of mercury. Of this number, 78 showed mean readings with an average of 119 mm. of mercury, while 43 showed extreme readings with an average of 158 mm. of mercury.

The average diastolic reading of the total number of 121 patients was 75 mm. of mercury, while 47 showed mean records which averaged 64 mm. and 74 showed extreme readings with an average of 82 mm. of mercury.

The average pulse pressure of the entire group of 121 patients was 58 mm. of mercury. Of the group, 67 patients showed mean readings with an average of 40 mm. of mercury while 54 patients showed extreme readings with an average of 68 mm.

If it is possible to interpret anything from these blood pressure readings, one could believe that there is a group represented by the 43 patients showing extreme systolic readings averaging 158 and mean diastolic readings of 64 in 47 patients in whom the disease produces an elevation of the systolic and depression of the diastolic pressure with an increase in the pulse pressure as in the 50 patients with an average pulse pressure of 93 mm. of mercury. This is frequently pointed out as characteristic of hyperthyroidism. However, this group comprises only about 37 per cent of the total number of cases of hyperthyroidism in this series while 63 per cent of those showing mean systolic readings of 119 and extreme diastolic readings averaging 82 with an average pulse pressure of 40 mm. of mercury demonstrate that at least the majority of the patients with a diagnosis of hyperthyroidism show essentially normal blood pressures.

It is more possible that this smaller group showing the higher systolic and lower diastolic readings is accounted for by the fact that approximately the same percentage of patients are found in the age group of 40 years or more, which is the time of life when essential or vascular hypertension is most prevalent.

Pulse Rates in Patients with Hyperthyroidism.—In determining the pulse rates of 178 patients, there being no records in 3 instances, we have determined (1) the average pulse rate at admission, (2) the lowest pulse rate during rest just before operation, (3) the maximum pulse rate after operation and (4) the pulse rate at the time of discharge of the patient. The average pulse rate at the time of admission for the entire group was 90 beats per minute, while in 88 showing mean pulse rates the average was 75 and for 90 patients who showed extreme pulse rates the average was 106. It is of interest that the group is practically divided into two equal parts according to the average mean or extreme pulse rates, with the difference of an average of 31 beats per minute, or in about one half of the patients the pulse rate at admission was normal while in the other half it was definitely elevated.

The average lowest pulse rate during rest before operation in the entire group of patients was 80, showing an average decline of 10 beats per minute through rest. The average low pulse rate during rest before operation of 39 patients who showed mean readings was 73 beats per minute, while in 139 patients who showed extreme rates the average was 82 beats per minute. It appears from these figures that there was a group of patients represented by the 39 or 22 per cent, showing an average mean pulse rate of 73 in whom the decline after rest was very slight, while in a larger percentage there was a definite decrease in the pulse rate after rest in bed.

The average maximum pulse rate after operation in the total number of patients was 103 beats per minute, while the average for a group of 47 patients, or 26 per cent, who showed mean readings was 92, and for 131 patients showing extreme readings it was 106. The similarity between these two groups and the groups showing low pulse rates during rest is so striking that it adds further evidence to the supposition that this series includes a rather large number of patients in whom the cardiovascular system was quite stable, even approaching the normal condition, and was influenced slightly if at all by the toxic condition as compared to the others.

The average pulse rate at the time of discharge of the entire 178 patients was 73, while in 45 who showed mean readings it was 68, and in 133 who showed extreme readings, 75.

The closely comparable divisional percentages obtained for the various pulse reactions of these patients in these last 3 groups is striking and suggests the possibility that the same etiologic factor might not have been operating in all these patients whose condition was diagnosed as toxic goiter.

The Incidence of Focal Infection.—The relationship of focal infection to hyperthyroidism has been so frequently observed and discussed

that it has even been considered as a causative agent, though it is not universally accepted as such. Unfortunately, we believe that this condition was not carefully searched for among this entire group. However, in the records we found sources of possible focal infection mentioned rather frequently but never mentioned as a possible etiologic factor. There was definite note made of infected teeth in 34 patients and of tonsillar infection in 27. The gallbladder was diagnosed as being diseased in 7 patients, while sinusitis was present in 3 and acute or sub-acute pelvic inflammatory conditions were considered present in 6 other patients of this group.

THE POSSIBLE PRECIPITATING CAUSES

Few patients ascribed the onset of their acute symptoms to a definite cause. There were eleven patients who associated the onset of their disease with immediately preceding acute infections while in three the onset of toxicity had been immediately preceded by an operation, one having been a tonsillectomy, another a hemorrhoidectomy and the third a pelvic operation. The most interesting precipitating cause and the most frequent was that of pregnancy, which was given as a cause by 12 women. There were 12 patients, or about 7 per cent of the total, who gave a history of having had previous thyroidectomies, some having had periods of fairly good recovery intervening while others had shown no improvement between operations, having undergone within a short time their second operative measure. Nine patients gave definite histories of acute trouble, the illness being diagnosed as nervous breakdown in the years preceding their operation. In 21 patients there had been a definite emotional shock antedating the onset of their symptoms.

THE OPERATIVE PROCEDURE AND MORTALITY

The most frequent operative procedure used on these 181 patients was a bilateral resection of both lobes of the gland, the actual amount or percentage of tissue removed not being stated in any record. A bilateral thyroidectomy was performed on 151 of the 181 patients. Adenomectomy was performed 4 times, while a subtotal resection of one lobe was performed 6 times and a total resection of one lobe 5 times. The ligation of one or more vessels as a preliminary operation was done in 2 patients, and the operative procedure was not stated in 9 instances.

Pathologic Report of the Tissue Removed.—A pathologic examination of the tissues removed by thyroidectomy was made in 151 instances; in 30 there was no examination reported. The diagnosis was colloid adenoma in 59 instances, while colloid adenoma with hemorrhage was reported twice, and with marked fibrosis in 17 specimens. Fetal

adenoma was reported 5 times, while adenomas, rapidly growing or cellular, were also reported 5 times. There was colloid adenoma with lymphoid hyperplasia and colloid adenoma with glandular hyperplasia reported respectively in 22 instances while colloid adenoma with lymphoid and glandular hyperplasia was reported 16 times. There was 1 instance each of chronic productive thyroiditis, adenocarcinoma and cystic colloid adenoma.

Mortality Rate.—Among the 181 patients operated on by the general surgical staff, 1 died while the patient was still on the operating table. This fatality was due to tracheal collapse, death being very sudden.

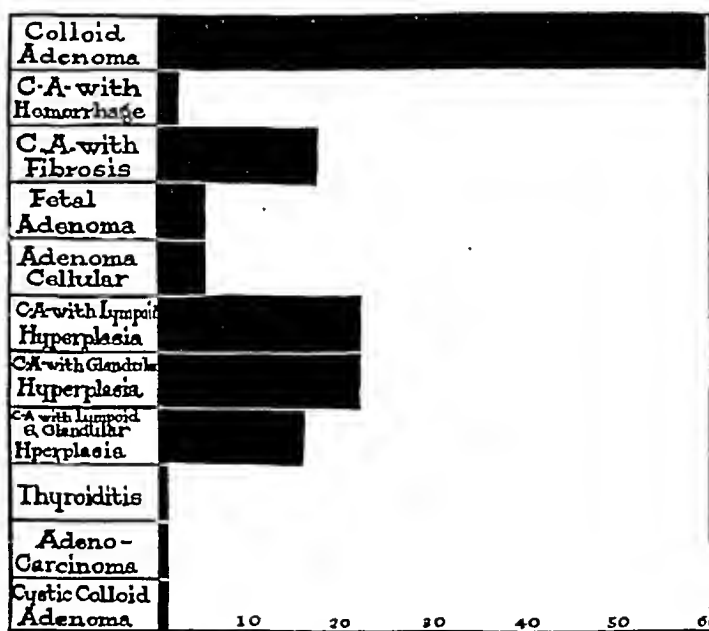


Chart 4.—Pathologic reports of thyroid tissue removed at operation, showing a predominance of the colloid adenomas with very few primary hyperplastic glands.

Nine other patients died within from twenty-four to thirty-six hours following removal of the thyroid gland, the operation being the direct cause of death in all. This makes a total mortality of 6 per cent following operation in the 181 cases of thyroidectomy. The mortality rate among those operated on by the more skilful and experienced surgeons was 2 per cent, but the general rate is raised by the death of patients operated on by the less skilled and experienced members of the department.

OPERATIVE RESULTS

Study of Seventy-Six Patients Two and One-Half Years After Thyroidectomy.—In the foregoing pages we have summarized the pertinent observations in 181 patients whose conditions were diagnosed

as toxic goiter before thyroidectomy. The present paper deals with the follow-up studies among the same group of patients after an average time of two and one-half years had elapsed after the operation. We encountered many difficulties in attempting to get in touch with these persons. The addresses of many were lost, but through letters and visits to homes and through diverse inquiries we were able to have 76 patients return for examination and basal metabolism tests. As we were strangers to most of these people, we had the advantage of being able to obtain their frank statements as to their operative results. From various experiences we believe that these people, at least in many instances, will not reveal their true condition entirely to the surgeon who operated on them. Likewise, we were able to approach their problems without bias and tried to offer no leading thoughts or suggestive questions in soliciting our information.

TABLE 1.—*Comparison of Preoperative Symptoms in Patients with Toxic Goiter with Those Present in a Group Two and a Half Years After Operation*

Symptoms of Toxic Goiter in 181 Patients Before Operation			Average 2½ Years After Thyroidectomy in 76 Patients		
Symptoms	No.	Per Cent	Symptoms	No.	Per Cent
Nervousness	156	86.0	Nervousness	32	42.0
Palpitation	138	76.0	Palpitation	28	37.0
Dyspnea	94	52.0	Dyspnea	7	9.0
Weakness	65	36.0	Weakness	48	63.0
Enlarged neck	58	32.0			
Perspiration	49	27.0	Perspiration	9	12.0
Nausea	40	22.0	Nausea	14	18.0
Irritability	37	20.0			
Choking	32	18.0	Choking	7	9.0
Vomiting	27	15.0	Vomiting	6	8.0
Diarrhea	24	13.0	Diarrhea	5	6.6
Dizziness	23	12.7			
Mental changes	21	11.5			
Edema	20	11.0	Edema	23	30.0
Exophthalmos	15	8.3			

We attempted to determine to what extent the symptoms that they had had before operation had persisted. This information was obtained by asking them to describe in what ways they felt different than before operation. No request was made for information as to specific symptoms. The following information regarding the symptoms was obtained.

The most frequent symptoms complained of, unlike those experienced before operation, was weakness, the second was nervousness and the third most commonly complained of symptom was palpitation. This varies from the incidence of symptomatic complaints before operation. Below are listed the various symptoms in order of frequency: weakness 48, nervousness 32, stronger 28, palpitation 28, edema 23, gas and bloating 19, nausea 14, sensitive to cold 10, perspiration 9, dyspnea 7, choking 7, rheumatism 7, vomiting 6, hoarseness 6 and diarrhea 5.

It is of interest that the same symptoms which were present before operation persist in such a high percentage of these people. A very interesting fact is the failure of over 50 per cent to regain normal strength and the rather frequent complaint of postoperative rheumatism with the number who complained of unusual sensitiveness to cold, edema and hoarseness. These symptoms indicate the presence of myxedema.

We believe that comparison of this table of symptoms with those before operation reveals the fact that the situation is not in line with what we desire from surgical intervention in toxic goiter.

Weight After Thyroidectomy.—In investigating the change or lack of change in the weight after operation we again found unexpected results. In these 76 patients who were operated on, 44, or 58 per cent, had gained and maintained their gain in weight two and one-half years after thyroidectomy. There were 7 who had lost weight and 25 whose present weight is practically the same as at the time of operation. This

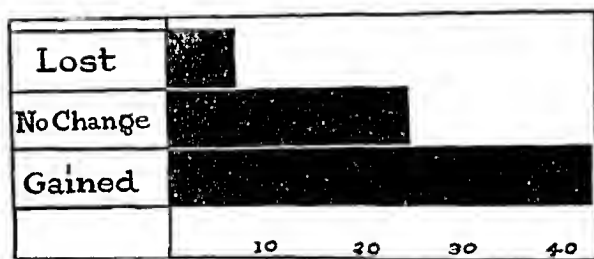


Chart 5.—The analysis of weights in seventy-six patients two and a half years after thyroidectomy showing a gain of weight in 58 per cent and loss or no change in 42 per cent.

makes a total of 32, or 42 per cent, for those who had lost, or who had shown no change in weight after thyroidectomy.

Pulse Rate After Thyroidectomy.—In determining the average pulse or heart rate, we have taken for comparison the average pulse rate for the same people at the time of their discharge from the hospital following thyroidectomy. We found that the average pulse rate in this group when they left the hospital was 80 beats per minute. The average pulse rate for this entire group now is 75, a slight decline in the total average. In obtaining the pulse rate of the means, we find this includes a group of 41 patients or 54 per cent with an average heart rate of 67, while the extremes consisted of a group of 35 patients or 46 per cent who showed an average heart rate of 86. The 41 or 54 per cent with low pulse rates of 67 closely parallels the number of patients, 58 per cent, who had gained weight, and likewise the 35 patients or 46 per cent with the average pulse rate of 86 is comparable to the 42 per cent who had lost, or had shown no change in their weight after thyroidectomy.

Basal Metabolic Test Records.—The basal metabolism reports of this group of patients, the test having been obtained on only 64 of the 76, was as follows: There were 7 who had basal metabolisms between -10 and -30 ; 43 showed a normal reading ranging between -10 and $+10$, 10 showed readings between $+10$ and $+20$, while 2 each showed readings between $+21$ and $+30$ and between $+31$ and $+40$.

Blood Pressure Observations.—In obtaining the average blood pressures of this group of patients, we also took for comparison the average blood pressure readings in this same group at the time of discharge from the hospital following thyroidectomy. We found that the average sys-

TABLE 2.—*A Comparison of the Mean and Extreme Pulse Rates After Operation Showing Close Correlation to the Percentage for Weights in the Group of Seventy-Six Patients*

At Time of Operation	No.	Rate	2½ Years After Operation	No.	Rate
General average of admission..	178	190	Average of group	76	76
Average of means	88	75	Average of means	41	67
Average of extremes	90	106	Average of extremes	35	86
Average low-resting rate.....	178	80			
Average of means	39	73			
Average of extremes	139	82			
Av. maximum after operation.	178	103			
Average of means	47	92			
Average of extremes	131	106			
Average of discharge	178	73			
Average of means	45	68			
Average of extremes	133	75			

tolic pressure for the group at the time of discharge from the hospital was 128 mm. of mercury, while the average for the same group now was 130 mm. of mercury, or practically identical results. The average diastolic blood pressure when leaving the hospital was 79 mm. of mercury and the average diastolic at present is 88 mm. of mercury. It is of interest that in the same group of patients there were 7 who showed a systolic blood pressure of 150 mm. of mercury or above at the time of discharge from the hospital while now there are 15. At the time of discharge from the hospital there were only 2 of the same patients with a diastolic reading of 100 mm. of mercury or over, while now there are 10 patients with abnormally high diastolic pressure, a relatively large increase in numbers over such a short period of time.

General Results of Thyroidectomy.—The most critical test of operative results depends on determining the general physical status of the patients a few years after. For this purpose we have grouped these patients under (1) those who are entirely well, (2) those showing

moderate improvement, (3) those showing slight improvement and (4) those in whom a definite thyroid toxicity has recurred and is present.

Our definition of those who are well is that the patient spontaneously expresses the same or as having been definitely cured by the operation; having none of the previous symptoms, or at least not more than one would expect in a normal person, and one in which they have gained strength and are not under the care of a physician at the present time.

We have classified as showing moderate improvement, those who express themselves in such statements as, "feeling better but the trouble is returning," or they feel that the operation has helped them, but they still have some of the symptoms and their strength is not good; also cases in which symptoms were evidently mild before operation and in which there had been no loss of weight; cases in which the few symp-

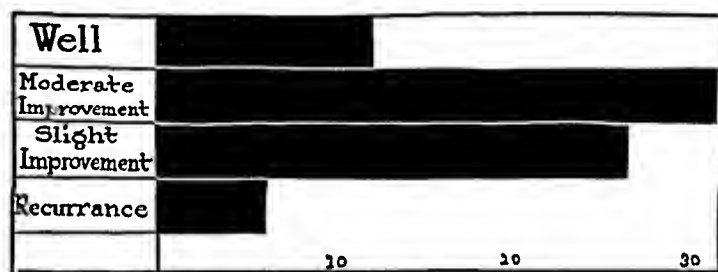


Chart 6.—The condition of seventy-six patients two and a half years post-operatively, according to our standards, shows 16 per cent cured, 40 per cent showing moderate improvement, 34 per cent showing slight improvement and a definite recurrence of toxicity in 10 per cent.

toms return periodically; cases in which the previous symptoms are better even though other symptoms have developed since, and the cases in which the patient feels, according to his statement, somewhat emotional and irritable, and those also in which the patient feels better but takes thyroid extract to maintain health.

In the group with slight improvement we have placed those patients who at the time of operation obviously had chronic nephritis or mitral stenosis, and whose symptoms still persist but are less severe; those whose general health is not good; those who evidently have a marked psychic background for the trouble, the symptoms of which still persist; those in whom there is yet a marked emotional instability; those who have a history of a nervous collapse since operation, and who are at present under the care of a physician for nervousness, heart trouble or psychiatric problems, and those who have been unable to work since the operation and have not gained weight or have lost it.

In the group of recurrence there is not only the typical picture of the toxic goiter syndrome, but also an elevated basal metabolic rate.

In the group classified as well, we found 12 patients, or about 16 per cent; of those showing moderate improvement there were 31 patients, or approximately 40 per cent; of those showing slight improvement there were 26, or 34 per cent; while there was a definite recurrence in 6, or 10 per cent. We can say, therefore, that there were 56 per cent of this group of patients who obtained sufficient relief from their thyroidectomy to enable one to classify them as average normal healthy persons, while there were 44 per cent in whom there was either a definite persistence or a recurrence of the condition, the persons not having obtained sufficient relief so that they might be considered well. In fact, many had noticed no improvement or are at present under the care of physicians for their original complaint. Again we find that these figures conform very closely to those previously mentioned in that we found 58 per cent had gained weight, whereas we noted that 56 per cent, approximately the same figure, had obtained definite weight while improvement, whereas 42 per cent had lost or shown no change in weight while 44 per cent showed slight improvement or a recurrence of their original symptoms.

Relationship of Glandular Pathology and Operative Results.—We attempted to determine whether there was any relationship between the improvement or lack of improvement and the nature of the glandular disease. The pathologic diagnosis showing the greatest incidence was colloid adenoma, there being but few with primary hyperplasia and an intermediate number showing colloid adenoma with some hyperplasia. We were unable to ascertain any relationship between improvement or lack of improvement in any of the patient's physical manifestations or present condition, with the type of pathologic process in the removed gland.

CONCLUSIONS

The immediate value of surgical intervention in acute hyperthyroidism cannot be denied, but its later benefit in all types of hyperthyroidism and the rationalism of its universal use are open to serious doubt. The methods that have been employed chiefly by surgeons in reporting their operative cures are also open to criticism. In our present confused state of knowledge concerning toxic goiter, it is essential that what information we have, whether etiologic or therapeutic, be well controlled and all sources of error, particularly such as personal factors and methods of procedure, be properly controlled and as accurate as possible. By using personal examinations instead of questionnaires, we have arrived at great accuracy and have been able to observe the many sources of error in other methods.

This study has clearly shown that all patients whose condition was diagnosed as hyperthyroidism do not conform to the same picture or manifest the same objective signs. A very important preoperative factor apparently is the patient's weight, a loss of weight being very important diagnostically and an easily obtained control for judging the probable benefit of surgical intervention. We found that 30 per cent, or almost one third, of all our patients had gained or shown no change in weight before operation, a very easily ascertainable and very important condition. In this series the same ratio, or 70 per cent losing weight and 30 per cent gaining or showing no change, was found in almost all the other clinical phases investigated. The definitely different classifications according to blood pressures, pulse rates and cardiovascular reaction to operation divided the series into two groups, the ratios very closely equaling those found for weights. Most important of all, these easily ascertainable preoperative observations are reflected in the postoperative results two and a half years later. Here we found that 42 per cent of the patients had failed to gain weight and 46 per cent showed a heart rate above normal. Also there were 44 per cent who showed but slight improvement or definite recurrence after thyroidectomy. In the postoperative group, consisting of less than one half of the entire preoperative number investigated, one cannot expect accurate approximation, but the different ratios and likewise the tendency to conformity are so striking that certain conclusions appear permissible. It is probable that the original diagnosis was erroneous in the group represented by the 30 per cent of patients who showed no loss of weight and consisted of those who manifested the toxic goiter cardiovascular syndrome but in whom the disturbance was due to a cardiac neurosis, psychiatric disturbance or other cause.

From the surgical point of view the amount of gland removed might not have been sufficient to produce the complete surgical result. It appears that weight might be a very important factor in the forming of a preoperative opinion.

It is of note that weakness persisted or was present in 63 per cent of the patients two and a half years after operation. Likewise edema, sensitiveness to cold, rheumatism and hoarseness were frequently complained of. It has been observed by Miller⁶ that operative cures of hyperthyroidism are accompanied by a high incidence of myxedema. The surgeons claim that the recurrence of toxic symptoms is due to the failure to remove sufficient of the thyroid gland. They are unable to state just how much to remove, this being left entirely to experience. It might be more accurate to state that good surgical results are obtained

6. Miller, J.: *Am. J. M. Sc.* **177**:98, 1929.

when the surgeon removes just enough of the thyroid tissue to leave the patient in a state of balance between hyperthyroidism and hypothyroidism. Might that not be the answer to the favorable results of thyroidectomy and that chance plays a part as to whether the patient will obtain the perfect balance that leads to health or be one of the 16 per cent in our series whom we found were well? Or might chance lead to the removal of too much of the gland and produce predominating myxedema of varying degrees, the severity varying and the requirements of thyroid extract differing with its severity? These people would be like our group of 40 per cent of patients or those showing moderate relief. Again, if too much gland is left, the disease persists as in our group of 10 per cent, while if an intermediate amount is removed, the toxic symptoms persist, hyperthyroidism being predominant, somewhat alleviated by a mild myxedema as in our group of 34 per cent. It appears probable to us that the surgical removal of thyroid tissue does not in any way strike directly at the cause of the disease hyperthyroidism as evidenced by the high percentage of persistent symptoms and the fact that relief is obtained only by the development of myxedema as revealed in the incidence of postoperative complaints and the necessity for a great many patients to continue to take thyroid extract. We believe that surgical intervention is substitutive therapy only and not curative. It substitutes the dominant disease myxedema for the less dominant disease hyperthyroidism, the degree of its results in accomplishing a clinical or symptomatic cure depending entirely on chance controlled somewhat by experience. Surgical removal in no way removes the cause.

In our present state of knowledge of hyperthyroidism, surgical intervention is of undeniable value but is used too indiscriminately. A patient should be carefully studied and an opinion concerning operation given only after a careful consideration of its possible benefits to the patient. We believe that operation should be looked on only as a temporary therapeutic agent which, though not satisfactory to a large percentage of patients, is our best present agency for acute cases. Results can be greatly enhanced by careful preoperative selection.

The failure of surgical measures to produce relief for more of these patients and the fact that its application is so lacking in careful control (its results depending only on the chance ability to substitute a proper or balanced myxedematous state) shows the necessity for further study, and that the problem is primarily one for the internist.

The disease hyperthyroidism is constitutional, and even in those considered cured by operation careful examination of the patient reveals stigmas of the disease persisting. Removal of the gland interrupts only one link in the general disease, the degree of its results resting on chance.

SUMMARY

1. One hundred and eighty-one cases of thyroidectomy have been studied according to the age of the patient, distribution and duration and incidence of symptoms. It was determined that 70 per cent of the patients lost weight while 30 per cent showed no change or even gained weight. The most common pathologic process in the thyroid was colloid adenoma, hyperplasia being much less frequent. The mortality rate was 6 per cent. The pulse rate at admission, minimum before and maximum after operation with the rate at discharge were ascertained. These showed a definite division into groups according to the mean and extreme rates, the ratios conforming closely to those observed for the weight changes.

2. Seventy-six cases were studied after an average elapsed time from operation of two and one-half years. Definite rules were adhered to, namely: (1) personal examination, (2) obtaining of basal metabolic rate, (3) avoidance of direct questions and (4) collection of data by some one else than the surgeon. A high persistence of the previous symptoms was found with also those symptoms suggesting prevalent myxedema. It was found that only 58 per cent of the patients had gained weight, that the pulse rate was below normal in a group approximating the same number who had gained weight and above normal in approximately the same number who had not gained weight since operation. The blood pressure showed an unusually high number who had developed abnormally high blood pressures since operation. We classified our patients as (1) well, (2) moderately improved, (3) slightly improved and (4) those with recurrence, according to definite rules. We found 16 per cent well, 40 per cent moderately improved, 34 per cent slightly improved and 10 per cent showed definite recurrences.

3. We consider surgical intervention unsatisfactory in a large group of these patients, but we consider that its benefits could be improved by more accurate preoperative selection, the weight being an accurate preoperative guide.

4. We consider surgical intervention only substitutional therapy, substituting the dominant myxedema for the less dominant state of hyperthyroidism and not in any way altering the real constitutional condition but only alleviating it. A perfect surgical result depends on the chance development of equilibrium between the hyperthyroidism and the developed myxedema.

5. The disease hyperthyroidism is primarily a problem of the internist, and its ultimate real cure will come through real control of the constitutional condition and not by surgically interrupting one link or substituting another less disturbing symptomatic or neutralizing disease.

POSTMORTEM BLOOD CHEMISTRY IN RENAL DISEASE *

S. H. POLAYES, M.D.

E. HERSHEY, M.D.

AND

M. LEDERER, M.D.

BROOKLYN

Many controversies over diagnosis arise at postmortem examinations in cases in which renal disease plays the leading or subsidiary rôle in the cause of death. Such disputes arise because of insufficient clinical data, a situation that frequently cannot be avoided because of varied adverse circumstances. However, in the absence of all other data, information concerning only the chemical changes in the blood is frequently of great aid in postmortem diagnosis. Unfortunately, in a good number of cases even this information is not available, and since the pathologist occasionally hesitates to make a diagnosis based entirely on the structural changes of the kidney, the final diagnosis often remains permanently in abeyance.

Experiences with several such cases have suggested to us the advisability of making a postmortem examination of the blood in the hope of securing aid in diagnosis in those instances in which the blood was not examined during life. A review of the literature on postmortem chemical examinations of the blood reveals a surprisingly scant amount of information. Authorities on legal medicine,¹ who undoubtedly often meet with these problems, fail to give enlightenment on this question. The only contribution in the literature dealing specifically with this subject is that of Paul,² who emphasized the value of postmortem determinations of blood urea nitrogen in estimating the terminal blood urea content ante mortem. This writer, however, presents too few figures for comparison between antemortem and postmortem observations to be at all convincing. On the other hand, he does make the important observation that during the first twenty-four hours after death, the urea nitrogen and creatinine content remain fairly constant. In connection with this observation, it is interesting to note that Sander,³

* Submitted for publication, Dec. 7, 1929.

* From the Department of Pathology of the Jewish Hospital of Brooklyn.

1. Personal communications from medical examiners office, New York.

2. Paul, J. R.: Postmortem Blood Chemical Determinations, *Bull. Ayer Clin. Lab.* **9**:51, 1925.

3. Sander, F. V.: The Preservation of Blood for Chemical Analysis, *J. Biol. Chem.* **58**:1, 1923-1924.

in a study on the preservation of blood for chemical analysis, found that the creatinine values of unpreserved blood remained constant for six days. A similar observation had been made previously by Falk and his co-workers.⁴

In the study of the cases presented in this paper, it has been our aim to compare the nonprotein nitrogen content of the blood (urea and creatinine) obtained before and after death in order to determine whether either one alone or both of the latter can be used as an aid in determining the renal status of the case. Specimens of blood were secured from the jugular vein or right atrium as early as possible within the first twenty-four hours after death, the body having been kept in the refrigerator from the time of its delivery to the morgue. Analyses were made in 100 cases representing various types of diseases, special efforts having been made to secure specimens from persons who died of a condition clinically diagnosed nephritis. Only those cases in which blood chemical tests were performed during life were selected, so that comparisons could be made between the postmortem and antemortem observations.

The hundred cases studied have been classified into five main groups; namely, miscellaneous diseases, acute infections, intestinal obstruction, renal disease with postmortem creatinine figures of less than 4 mg. per hundred cubic centimeters of blood and renal diseases with post-mortem creatinine figures of 4 mg. or more. Acute infections and intestinal obstruction have been grouped separately, because it has been frequently stated that there is a retention of nonprotein nitrogen in these cases just before death.

The time that elapsed between the death of the patient and the securing of blood for analysis ranged between one-half to twenty-four hours, the average being six and one-half hours. With few exceptions, the analyses were made immediately after the blood was secured. In no case was the examination delayed for more than ten hours, the specimen having been kept in the refrigerator during the delay.

The intervals between the examination of blood obtained post mortem and that obtained during life ranged from one hour to sixteen weeks, the average being about thirteen days. In very few cases, however, was the interval less than one day or more than two weeks.

Whenever other tests of renal function were performed, the results were recorded. The tests consisted of estimations of the phenolsulphonphthalein excretion, urea concentration tests and the diazo reaction⁵ in the blood.

4. Falk, K. G.; Baumann, E. J., and McGuire, G.: *The Chemical Investigation of Spoiled Meat*, J. Biol. Chem. **37**:525, 1919.

5. Andrews, E. H.: *An Unexplained Diazo-Color Reaction in Uremic Sera*, Lancet **1**:590, 1924.

TABLE 1.—*Analysis of Data on One Hundred Cases*

Group	Type of Disease	No. of Cases	Number of Hours Postmortem Specimen Was Secured		Interval Between Postmortem and Antemortem Determination		Renal Function Tests	Antemortem Determinations, Mg. per 100 Cc. Blood			Postmortem Determinations, Mg. per 100 Cc. Blood		
								Creatinine		Urea	Creatinine		Urea
			Range	Average	Range	Average		Range	Average		Range	Average	
I	Acute infections.....	15	1 to 24	11.2	9 hr. to 22 days	5 days	Range 65% record in 1 case Average 65%	1.2 to 2.9	1.8	10.2 to 45.0	1.7 to 3.6	2.2	19.2 to 65.0
II	Miscellaneous diseases.....	51	1 to 24	6.2	3 hr. to 16 wk.	16 days	P.S.P. 67% 40% to 83%	1.1 to 4.2	1.6	9 to 83	1.4 to 3.3	2.3	11.4 to 98.5
III	Intestinal obstruction.....	4	3 to 9	6.5	5 to 12 days	6.5 days	None done	1.3 to 2.5	1.8	12.6 to 31.2	2.9 to 3.8	3.3	32.8 to 52.1
IV	Renal diseases with postmortem creatinine determinations of less than 4 mg.	16	1 to 15	4.8	1 hr. to 30 days	12.6 days	None done	1.2 to 3.1	1.9	11.4 to 71.4	1.7 to 3.7	2.6	12.6 to 83.8
V	Renal diseases with postmortem creatinine determinations of 4 or more mg.	14	½ to 15	4.9	2 to 150 days	16 days	P.S.P. traces in 4 cases; diazo test* on blood positive in 2 cases antemortem and 2 cases postmortem	3 to 10.0	5.6	32 to 125	4.1 to 12	7.3	50 to 192

* Polayes, S. H.; Lederer, M., and Fradkin, W. Z.: Observations on the Diazo Test in Nephritis, J. Lab. & Clin. Med. 14: 229, 1923.

Autopsies were performed in 40 per cent of the cases. Those showing gross or microscopic evidences of renal changes were placed in the renal disease groups regardless of the blood determinations.

ANALYSIS OF DATA

Urea.—It will be noted from table 1 that the greatest blood urea content occurred post mortem in the disease group showing the highest blood creatinine values at autopsy, namely, in the group of renal diseases, in which average creatinine values of 5.6 were obtained ante mortem. Next in order follow the other group of renal diseases, intestinal obstruction, acute infections and the miscellaneous group. Great differences were noted, however, between the urea nitrogen determinations on the blood specimens obtained before and after death. It at once became apparent, therefore, that postmortem determinations of urea would be of no value as an aid in determining the degree of retention during life. Thus, case 15 showed 55.5 mg. of urea per hundred cubic centimeters of blood post mortem as compared to 15.5 mg. six days prior to death. Similarly, case 49 with a urea reading of 11.4 mg. twelve days before death showed a postmortem determination of 62.5 mg. Similar examples were found in thirty-four other cases. The reverse was also found to be true. In six cases, the urea values during life exceeded those obtained on postmortem examination. Thus, in case 24, the postmortem determination of urea showed 34.5 mg. per hundred cubic centimeters of blood, while the values obtained two days before death were 83.3 mg. These observations show the unreliability of postmortem determinations of urea as an index of the urea content of the blood ante mortem.

The determination of an arbitrary figure above which all cases are to be considered as falling into the group of renal insufficiency (as will be described with creatinine) is also impossible. This is true because higher urea figures have been found in some cases that presented no evidence of renal disease clinically or anatomically than were found in some frank cases of uremia.

Creatinine.—A study of table 1 shows that postmortem there is an average rise in the creatinine figures of from 0.5 to 1.7 mg. over those which were obtained during life. The lowest average postmortem figures (2.2 mg.) were obtained in the group of acute infections; the highest (7.3 mg.), in the group of renal diseases. Blood specimens from patients with intestinal obstruction yielded average creatinine figures (3.3 mg.) that were higher than those obtained from the miscellaneous group (2.3 mg.). They were even higher than those found in the first group of renal diseases (2.6 mg.).

TABLE 2.—*Renal Diseases with Postmortem Creatinine Figures of Four or More Milligrams per Hundred Cubic Centimeters of Blood*

Case	Diagnosis	Autopsy	No. of Hours Post- mortem Specimen Was Received	Interval Between Antemortem and Postmortem Determi- nations	Renal Function Tests and Other Tests Indi- cating Renal Status	Creatinine in Mg. per 100 Cc. of Blood	
						Ante- mortem	Post- mortem
6	Acute nephritis, uremia	Yes	1	6 hours	5.0	5.0
15	Verrucose endocarditis amyloid degeneration of kidneys; thrombosis of left renal vein	Yes	2	6 days	5.0	7.8
17	Uremia.....	No	1	4 days	Positive diazo reaction on the blood post mortem	6.0	6.0
22	Chronic glomerular nephritis	Yes	2	5 mo.	No creatinine determi- nation was made later than 5 months before death, but a chemical analysis made 1 month before death showed the following: total nitrogen, 1.26 Gm.; total protein, 5.52%; nonprotein nitro- gen, 377 mg.; the blood diazo test ante mortem was also positive; the phenolsulphonphthalein was 14% a year before death	3.0	7.5
23	Acute, subacute and chronic glomerulo- nephritis, with termi- nal uremia	Yes	2	10 days	Phenolsulphonphthalein test showed faint traces of the dye	6.0	10.0
32	Hypertension; chronic nephritis	Yes	3	30 days	Phenolsulphonphthalein test showed traces of the dye	3.0	4.1
45	Pyelonephrosis ne- phrotomy; uremia	No	8	4 days	Phenolsulphonphthalein test showed faint traces of the dye	6.0	4.2
58	Arteriolar sclerosis of kidney uremia	Yes	3	4 days	Blood diazo positive ante mortem	7.1	9.4
71	Pyonephrosis	No	8	4 days	3.3	6.0
83	Pyonephritis	Yes	5	2 days	Phenolsulphonphthalein test, 11%	7.0	9.1
84	Cirrhosis of liver; chronic nephritis; uremia	No	6	2 days	Blood diazo positive ante mortem	5.0	7.0
86	Malignant nephro- sclerosis; hyperten- sion; uremia	No	4	4 days	Blood diazo positive nine days before death	10.0	10.0
98	Malignant nephro- sclerosis; hyperten- sion; uremia	No	15	5 days	5.0	5.2
99	Mercuric chloride poisoning; acute and subacute nephritis	Yes	12	8 days	Blood diazo positive six days before death	8.5	12.0

A study of table 2 shows that readings of 4 mg. or more per hundred cubic centimeters of blood were found only in cases of renal insufficiency as determined clinically at autopsy and by the other renal function tests mentioned. Furthermore, when the creatinine content post mortem was 4 mg. or over, the figures obtained during life were over 3 mg., which is universally accepted as definite evidence of severe impairment of renal function. Thus, in the group of renal diseases previously tabulated, which yielded postmortem figures for creatinine ranging between 4.1 and 12 mg. (average 7.3 mg.), the values during life ranged between 3 and 10 mg. (average 5.6 mg.) No such high figures were obtained ante mortem in any of the other groups, including that group of renal diseases in which the postmortem values were less than 4 mg. per hundred cubic centimeters of blood. Therefore, it may be concluded that although not all cases of renal disease clinically or anatomically show high blood creatinine figures post mortem, the finding of 4 mg. or more per hundred cubic centimeters of blood after death indicates that high figures (3 mg. or more) existed during life, and that there must have been a condition of severe renal insufficiency.

COMMENTS ON GROUPS OF TABLE 1

I. Autopsies were performed in six cases of this group. The conditions in these cases included lobar pneumonia and bronchopneumonia, meningococcic meningitis, agranulocytic angina, bacterial endocarditis and bacteremia.

II. Autopsies were performed in sixteen cases of this group. The 4.2 mg. of creatinine noted occurred in only one case. This case was one of syphilitic endocarditis, and no evidence of renal dysfunction was found. The next highest reading was 2.9 mg.

III. Autopsies were performed in two cases of this group; neither revealed any renal disease.

IV. Autopsies were performed in eight cases of this group, and renal disease was found in all. Neoplastic thrombi in large renal vessels with infarctions were found in two cases, pyonephrosis in two and arteriosclerosis in three. The rest gave clinical evidence of renal disease but showed no nonprotein nitrogen retention in the blood.

V. Autopsies were performed in eight cases of this group. Three of these showed severe acute or chronic glomerulonephritis; one showed pyonephritis; one, thrombosis of the main renal vein; one, severe arteriosclerotic kidneys, and one, mercuric chloride poisoning. The remaining six cases were all clinically classic cases of severe renal insufficiency in which death was due to uremia.

CONCLUSIONS

From a postmortem study of the creatinine and urea contents of the blood specimens in 100 cases, the following conclusions may be made:

1. Blood creatinine determinations are often helpful as an aid in determining the status of the renal function during life.
2. The urea values are not as helpful as the creatinine figures.
3. A creatinine content of 4 mg. or more per hundred cubic centimeter of blood obtained post mortem indicates marked creatinine retention during life and therefore severe renal insufficiency.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

I. CONCENTRATION OF NONPROTEIN NITROGENOUS CONSTITUENTS IN THE BLOOD *

A. MAURICE WAKEMAN, M.D.

AND

CLARE A. MORRELL, M.A.

NEW HAVEN, CONN.

The work on metabolism in yellow fever which is reported in this and in subsequent articles was carried out from March 15, 1928, to May 6, 1929, for the Yellow Fever Commission of the Rockefeller Foundation at Lagos, Nigeria.

When the work was practically completed, but before it was prepared for publication, Dr. A. Maurice Wakeman contracted an illness which ended fatally before his return to this country. Publication work has, therefore, been carried out entirely by the junior author. In the course of planning the studies and conducting the experiments, Dr. Wakeman had ample occasion to express his views as to the significance of the data obtained and every attempt has been made to present the material in accordance with his views.

It was hoped that there would be human material available for investigation, but by the time the studies were begun, the epidemic of yellow fever in Nigeria had subsided. Stokes, Bauer and Hudson, however, had demonstrated that Indian monkeys, *Macacus rhesus*, were susceptible to the disease; and Hudson¹ has shown that the pathologic lesions produced by the disease in the monkey are quite similar to those which have been demonstrated in human autopsies. The studies were, therefore, conducted entirely on experimentally infected *Macacus rhesus* monkeys, of which an adequate supply was available. Because in both human beings and monkeys the major pathologic lesions of the disease have been found in the liver, greater attention was given to the study of those chemical and metabolic functions which are known to be influenced mainly by the liver. However, attention was not entirely diverted from other functions and those of the kidney were especially noted.

* Submitted for publication, Jan. 30, 1930.

* From the laboratory of the West African Yellow Fever Commission of the International Health Division, Rockefeller Foundation, Lagos, Nigeria.

1. Hudson, N. P.: Am. J. Path. 4:395, 1928.

The present paper deals with the nitrogen metabolism and the concentration of nitrogenous substances in the blood during the course of yellow fever. It has been demonstrated that in the terminal stages of the disease, the faculties of deaminizing amino-acids to acid-forming urea, functions which are now known to reside chiefly if not entirely in the liver, are greatly impaired.

The technics employed in the management of monkeys throughout these investigations are described in this article and will be used for reference in subsequent papers of this series.

A search of the literature has revealed no studies of the chemistry and metabolism of yellow fever which are significant. Urinalyses for a variety of substances were made by Penido² but, owing to the absence of any attempt at dietary control, cannot be interpreted.

EXPERIMENTAL METHODS

Treatment of Animals: Diets.—The animals used in these experiments were Indian monkeys, *Macacus rhesus*, weighing between 1.5 and 4 Kg. The heavier animals were selected to facilitate the obtaining of reasonably large quantities of blood. Those that were being used for experimental work were kept in individual cages.

The monkeys were fed in either of two ways. In experiments in which regulation of diet or collection of samples of urine was unnecessary, the usual animal house food was given in three meals a day. Breakfast consisted of one of the following combinations: (1) sugar cane, 45 Gm.; casava, 45 Gm.; (2) sugar, 40 Gm.; tiger nuts, 7 Gm.; corn, 7 Gm.; (3) sugar cane, 50 Gm.; rice, 45 Gm.; water, 100 cc.; or (4) sugar cane, 50 Gm.; tiger nuts, 7 Gm.; peanuts, 7 Gm.; water, 100 cc. Lunch was composed of 20 Gm. of bread and 100 cc. of condensed milk. Supper included 20 Gm. of corn, half of one hard-boiled egg, half an orange, 20 Gm. of peanuts and 100 cc. of water. The food was placed in small metal dishes and thrust into the cages, where the monkeys ate as much of it as they wanted.

For the purpose of regulating the nitrogen and carbohydrate intake in the metabolism experiments, a special liquid diet which could be fed by a stomach tube was used. Feeding in this manner eliminated the possibility of contamination of urine and feces with the diet and made it possible to measure and regulate the amount of food given. At first a semisolid mixture containing minced bananas and peanuts was used, but since this combination was extremely difficult to force through the stomach tube, it was abandoned.

Diet no. 1, which was used throughout the experiment with *M. rhesus* M 1, consisted of the following combinations: 600 cc. of unsweetened evaporated milk, 150 cc. of orange juice, 300 Gm. of cane sugar and 4 Gm. of salt (NaCl) made up to 1,220 cc. with water. Analysis of this diet showed it to contain 4.18 Gm. of protein and 0.435 Gm. of chloride (as NaCl) per hundred cubic centimeters. The monkey was fed 60 cc. twice a day, making a total of 210 calories with 810 mg. of nitrogen and 520 mg. of sodium chloride.

2. Penido, J. C. N.: *Suplemento das Memorias Instituto Oswaldo Cruz, Febre Amarella*, no. 2, 1928, p. 65.

In view of the positive nitrogen balance which persisted throughout the normal period in *M. rhesus* M1, it was concluded that this diet contained more nitrogen than the animal had received in the regular diet.

Diet no. 2 was designed to reduce the protein intake. It consisted of the following ingredients: evaporated milk, 400 cc.; orange juice, 150 cc.; cane sugar, 350 Gm.; sodium chloride, 4 Gm., made up to 1,220 cc. with water. Animals were fed 60 cc. of this combination morning and night, the total containing 530 mg. of nitrogen and yielding 202 calories.

Diet no. 3 was made to reduce the nitrogen intake still further. It was made as follows: evaporated milk, 300 cc.; orange juice, 150 cc.; cane sugar, 300 Gm.; sodium chloride, 4 Gm., made up to 1,100 cc. with water; 120 cc. of this diet yielded 447 mg. of nitrogen and 200 calories.

When it was desired to study changes occurring in the urine during the course of the disease, the animals were fed on one of these diets, the urine and stools were analyzed and periodic blood studies were made.

Special cages were constructed which made it possible to collect all of the urine and feces. The cage consisted of wooden framework, 3 feet wide, 3 feet long and 2 feet high, covered with a wire grating and supported by four legs about 14 inches above the ground. One side opened as a door. It was provided with a movable wire grating on which the monkey rested and which caught the feces. Immediately below this was a pyramidal tin tray which caught the urine. This was also removable and, with the grating, could be slid in or out in grooves directly below the cage door. There was a small spout in the bottom of the tray to which a wide mouthed 100 cc. bottle was attached by means of a rubber stopper. The whole cage was made mosquito-proof by covering it with 20-gage copper wire netting.

Monkeys to be used in metabolism experiments were transferred from the runways to these cages and fed on standard diet from five days to several weeks before studies were commenced. This preliminary period served to establish the monkeys on a more or less constant nitrogen excretion and to accustom them to the diet and handling. Any animal that developed diarrhea was at once discarded. The care of the animals, feeding, cleaning and collecting excrement, was carried out by native boys under our supervision.

Collection of Excreta.—The daily routine commenced at 8 a. m. At that hour the monkey was induced to void any urine which happened to be in the bladder. This could be done almost every time by simply catching hold of the monkey. The bottle containing the specimen was then replaced by a fresh one. The bottle with the morning urine was labeled, stoppered and placed on ice to be analyzed as part of the preceding twenty-four hour excretion. The monkeys were then removed from the cage. After the rectal temperature had been recorded and the monkeys' fur brushed thoroughly to remove any loose hair or dandruff, they were fed the special diet by stomach tube. The procedure of feeding was carried out by thrusting a wooden gag with a hole in the center between the teeth and gently forcing a small soft rubber catheter down the esophagus. A 100 cc. syringe containing the measured quantity of the diet was attached to the catheter. The weight of the plunger was sufficient to force the liquid into the stomach. In monkeys which came to autopsy after long periods of forced feeding, no erosion of the esophagus or stomach was observed. At 8 a. m. and 5 p. m., the collection tray was washed with about 40 cc. of distilled water and the washing collected in a separate bottle. The 8 a. m. washing was analyzed with the urine obtained the previous day. At 5 p. m., the monkey was removed from the cage, fed and brushed, and the temperature taken as before. This time, after the tray

had been washed with distilled water, it was taken out, thoroughly scrubbed with a brush, first with tap water and then with distilled water, and afterward dried.

The urine was divided into two classes; that excreted from 8 a. m. to 8 p. m. was labeled day urine and that from 8 p. m. to 8 a. m., night urine. The bottles were removed after each voiding, marked, stoppered and put on ice to await analysis. A few drops of toluene were added to each bottle before it was attached to the collection tray. The animal was offered additional water at 12 o'clock noon, and the amount drunk was recorded.

The accuracy with which the total amount of nitrogen excreted could be recovered by this method of collection and washing was checked. An artificial urine solution was made which contained a known quantity of urea and ammonium sulphate. Quantities amounting to 50 cc. of this solution, containing 84.4 mg. of nitrogen, were sprayed over a collection tray at three hour intervals for ten hours. Only 37 cc. of the 50 cc. of liquid was recovered immediately. The tray was washed with 50 cc. of water and the artificial urine and washings made up to 100 cc. This was analyzed for total nitrogen content by the macro-Kjeldahl method. In one experiment an average of 86.4 mg. of nitrogen was recovered. In another experiment in which the collection extended over twenty-four hours, an average of 83.1 mg. of nitrogen was found.

In the course of the metabolism experiments with two monkeys, several months after this routine for collecting urine was established, it was found that little or no urea nitrogen could be recovered from their urine while the ammonia nitrogen had greatly increased. Only after washing the cages thoroughly with lye and a compound solution of cresol did the amount of urea and ammonia nitrogen excreted return to a normal level. It was evident that the urine had been contaminated with some organism capable of converting the urea nitrogen to ammonia, in spite of the presence of toluene.

At the conclusion of the twenty-four hour period, the various bottles of day urine were mixed, and the volume and the reaction to litmus were noted. The night urine was treated in a similar way. The individual collecting bottles were rinsed with wash water and the rinsings added to the urine. The day and night urines were combined and mixed thoroughly. After the volume had been recorded, the urine was filtered to remove any hair or dirt which might have collected on the tray of the cage. The residue was usually very small, and was analyzed on several occasions for nitrogen. The average nitrogen content of four such residues was 3 mg.

In one case it was attempted to mark off the stool periods by giving powdered charcoal with the morning feeding. This method proved unsatisfactory, since the charcoal appeared in the feces about thirty-six hours later and continued to be excreted for several days. After this, whatever was excreted during the day was collected and transferred to a bottle containing a weighed quantity of concentrated sulphuric acid. The stool periods were commenced and ended twenty-four hours after the urine periods. The bottle containing the excrement for a period was thoroughly mixed by shaking and an aliquot analyzed for total nitrogen by the macro-Kjeldahl technic. The total amount of nitrogen was calculated and divided by the number of days in the period to give the daily excretion. As a rule, the animals had two formed stools a day, of putty-like consistency, yellowish brown, an inch long and about the diameter of a lead pencil.

The metabolism studies were divided, for the purpose of comparison, into a preliminary period during which complete analyses were not made; a normal control period; a yellow fever period, and, in the case of the animals which recovered from the disease, a recovery period. The lengths of the periods were

regulated by the temperature chart, the time of infection and the clinical appearance of the monkeys.

Collection and Analyses of Blood.—Blood samples were collected from the saphenous vein in the leg, from an arm vein, or from the heart. Since cardiac punctures were liable to cause hemopericardium, resulting in the death of the animal, this technic was never used if it could be avoided. When large amounts of blood were taken, the femoral artery or vein was exposed under local anesthesia. Experience proved that a vein in the arm was the most satisfactory to use in drawing moderate amounts of blood. From 5 to 10 cc. of blood could usually be obtained from this vessel. During the last hours of life, it was often extremely difficult to obtain more than 1 cc. of blood from any vein. This appeared to be due to the pronounced fall in blood pressure which accompanied the prostration of the animal. In these cases cardiac puncture was resorted to.

In drawing blood from the arteries during yellow fever, special precautions against spurters were taken. A framework with a glass top was placed over the animal, and the manipulations were carried out under this. The glass presented an effective screen against blood being thrown up into the face, without hiding the field of operation. In handling all virulent material, rubber gloves were worn and supplemented during more complicated operative procedures with rubber sleeves and apron. Blood used for nitrogen determinations was collected in a clean dry syringe, transferred to a small flask and shaken with a few milligrams of lithium oxalate to prevent clotting. About 1 mg. of lithium oxalate per cubic centimeter of blood was used. For electrolyte studies, the blood was collected in a syringe under mineral oil and the serum separated with anaerobic precautions by the technic of Austin and his co-workers.³

Analytical Methods.—The proteins of the blood were precipitated by the tungstic acid method of Folin and Wu.⁴ The nonprotein nitrogen was determined by Folin's micro-Kjeldahl digestion followed by direct nesslerization of the digestion mixture.⁵ Amino-acid nitrogen was estimated by the colorimetric method of Folin.⁶ The uric acid values were obtained by Folin's direct method,⁷ with Folin and Trimble's phosphotungstic acid reagent.⁸ Folin's method⁹ for creatinine was employed, with pure creatinine as the standard and trinitrophenol purified according to the technic of Folin and Doisy.¹⁰ Ergothioneine was determined by Hunter's¹¹ method. Ammonia was estimated by Folin's technic.¹² Benedict's¹³ method for blood sugar was used. Phosphorus was determined by the method described by Fiske and Subbarow,¹⁴ and chlorides by the method of van Slyke.¹⁵ Bile pigments were estimated by the van den Bergh technic.¹⁶

3. Austin, J. H.; Cullen, G.; Hastings, A. B.; McLean, F. C.; Peters, J. P., and Van Slyke, D. D.: J. Biol. Chem. **54**:121, 1922.

4. Folin, O., and Wu, H.: J. Biol. Chem. **38**:81, 1919.

5. Folin, O., and Wu, H.: J. Biol. Chem. **38**:90, 1919.

6. Folin, O.: J. Biol. Chem. **51**:377, 1922.

7. Folin, O.: J. Biol. Chem. **54**:153, 1922.

8. Folin, O., and Trimble, H. C.: J. Biol. Chem. **60**:473, 1924.

9. Folin, O., and Wu, H.: J. Biol. Chem. **38**:98, 1919.

10. Folin, O., and Doisy, E. A.: J. Biol. Chem. **28**:349, 1917.

11. Hunter, C.: Biochem. J. **22**:4, 1928.

12. Folin, O., and Denis, W.: J. Biol. Chem. **11**:534, 1912.

13. Benedict, S. R.: J. Biol. Chem. **68**:759, 1926.

14. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.

15. Van Slyke, D. D.: J. Biol. Chem. **58**:523, 1923.

16. McNee, J.: Quart. J. Med. **16**:390, 1923.

Urea nitrogen in the blood was in some cases estimated by hydrolysis with urease, aeration of the ammonia into standard acid and nesslerization. Owing to a very uncertain air current this method proved unsatisfactory, and in the absence of any source of heat for distillation which could be regulated the following procedure was adopted: Ten cubic centimeters of the blood filtrate was transferred to a 50 cc. volumetric flask which had been rinsed first with 10 per cent nitric acid and distilled water. After the addition of 1 cc. of a freshly prepared 10 per cent solution of Squibb's urease powder, the mixture was allowed to stand at room temperature (30 to 35 C.) for twenty minutes. One and a half cubic centimeters of washed, dust-free permutit powder was added from a graduated 15 cc. centrifuge tube, after having been tapped down to the mark. The flask was agitated gently for five minutes and the permutit powder washed by decantation with 100 cc. of distilled water; 10 cc. of water and 0.5 cc. of 10 per cent sodium hydroxide were then added, followed by enough water to bring the volume to about 40 cc. After the addition of 5 cc. of Nessler's solution the whole was made up to volume. The standard was prepared as follows: Into a 100 cc. volumetric flask which had been washed with nitric acid and water, 20 cc. of distilled water was introduced, followed by 2 cc. of the urease solution. After the solution had stood twenty minutes, 3 cc. of the permutit powder was dropped in and the flask agitated gently for five minutes. After washing and the addition of a double quantity of water, 1 cc. of 10 per cent sodium hydroxide was run in, followed by 3 cc. of a standard ammonium sulphate solution containing 0.1 mg. of nitrogen per cubic centimeter. The solution was diluted to 80 cc. with water, 10 cc. of alkaline potassium mercuric iodide test solution (Nessler's reagent) poured in, and the whole brought up to volume. Standards and blood filtrates were treated simultaneously.

Analysis of Urine.—Urine was analyzed for total nitrogen by Folin's method of direct nesslerization¹⁷ and, when the quantity permitted, this method was checked by macro-Kjeldahl digestion and titration with 0.05 normal acid and alkali. Amino-acid nitrogen was determined by the colorimetric procedure of Folin¹⁸ and ammonia by the method of Folin and Bell.¹⁹

For uric acid, the precipitation technic of Folin and Wu²⁰ was used. Creatinine was determined by the method of Folin²¹ and phosphorus by that of Fiske and Subbarow;¹⁴ chlorides were estimated by the Volhard-Harvey²² procedure, and organic acid by the titration described by Van Slyke and Palmer.²³

The protein was estimated in some cases by means of an albuminometer and Esbach's reagent, and in others by determining total nitrogen before and after precipitating the protein with tungstic acid, and multiplying the difference by 6.25. A solution of sodium nitroprusside was used for qualitatively testing for acetone in a few specimens of urine. The qualitative tests for sugar were performed with Benedict's solution.

Urea was determined by a slight modification of the Folin and Youngburg method,²⁴ because the original technic often yielded cloudy or greenish colored

17. Folin, O., and Denis, W.: J. Biol. Chem. **26**:473, 1916.

18. Folin, O.: J. Biol. Chem. **51**:393, 1922.

19. Folin, O., and Bell, R. D.: J. Biol. Chem. **29**:329, 1917.

20. Folin, O., and Wu, H.: J. Biol. Chem. **38**:459, 1919.

21. Folin, O.: J. Biol. Chem. **17**:469, 1914.

22. Harvey, S. C.: The Quantitative Determination of the Chlorids in the Urine, Arch. Int. Med. **6**:12 (July) 1910.

23. Van Slyke, D. D., and Palmer, W. W.: J. Biol. Chem. **41**:567, 1920.

24. Folin, O., and Youngburg, G.: J. Biol. Chem. **38**:111, 1919.

solutions on nesslerization. At first an alcoholic extract of jack bean was made, but later this was replaced by Squibb's urease powder. The urease reaction was carried out in a 250 cc. volumetric flask that had been rinsed previously with nitric acid and distilled water. The ammonia nitrogen was either removed beforehand with permutit or both determined together and the ammonia nitrogen subtracted from the total. Enough urine to contain approximately 1 mg. of urea nitrogen was transferred to the flask with 10 cc. of water and 1 cc. of freshly prepared 10 per cent urease solution. After the mixture had stood for twenty minutes at room temperature (30 to 35 C.), 3 cc. of dust-free permutit powder was added. This was measured in a 15 cc. conical graduated centrifuge tube. The tube was tapped on the desk two or three times to shake the powder down to the mark. After the addition of the permutit powder, the flask was swirled for five minutes and the powder washed, by decantation, with about 200 cc. of distilled water; 10 cc. of water and 1 cc. of 10 per cent sodium hydroxide were then run in, the flask was gently agitated from three to five minutes, and the contents made up to 200 cc.; 20 cc. of Nessler's solution was added and the whole made up to volume with water. The standard was treated in precisely the same manner except that an equal quantity of water was used in place of the urine and 1 cc. of an ammonium sulphate solution containing 1 mg. of nitrogen was added after bringing the volume to 200 cc. with water.

The accuracy of this method was tested with standard urea and ammonium sulphate solutions. From 97 to 100 per cent of the theoretical amount of urea nitrogen was recovered.

Clinical Observations.—Clinical manifestations in the *rhesus* monkeys infected with yellow fever virus have been described by Stokes, Bauer and Hudson.²⁵ A brief résumé with a few additional remarks is given here. The animals used in this work were infected with blood virus or liver emulsion or by a mosquito bite. Stokes, Bauer and Hudson found the average incubation period in the monkeys bitten by mosquitoes to be between three and four days, and in those inoculated with blood virus between two and three days. Rectal temperatures were taken twice a day, between 8 and 9 a. m. and 4 and 5 p. m. After a consideration of the normal temperatures of a large number of monkeys, any temperature of 104 F. or over was taken as an indication of fever, an arbitrary standard which was not always satisfactory. Occasional temperatures of 104 F. or more were observed in normal animals. On the other hand, in some monkeys with normal temperatures as low as from 100 to 101 F., the temperature during the course of the disease never rose as high as 104 F.

The course of the fever showed considerable variation in different animals. Some had a very short course while in others fever persisted over a period of a week or more. In some monkeys there was a return to normal or even subnormal temperature after a short period of fever, followed by a terminal rise. In a great many cases, the temperature during the last few hours of life was subnormal.

During the incubation period and usually during the first day of fever, no indications of illness were evident. If the febrile period was short and terminated in the death of the animal from two to three days after the onset of fever, symptoms were usually apparent on the second day. The animals became listless and required greater stimuli to rouse them to activity. On the last day of life they were found lying down and unresponsive to any movement of their cages, giving every appearance of being unconscious of their surroundings.

25. Stokes, A.; Bauer, J. H., and Hudson, N. P.: *Am. J. Trop. Med.* 8:103, 1928.

In nineteen cases observed no food was taken for from seven to eighteen hours and, in one case, thirty-six hours before death. In every case the last meal taken was milk or orange juice, the solid part of the diet being refused. Twelve animals were found lying down or prostrated from seven to twenty hours before death; four were feebly sitting up. No observations were made on the remaining three.

The monkeys usually drank water after they had refused all food, in several instances consuming as much as 100 cc. at one time. Three of the monkeys used in the metabolism experiments vomited during the febrile period, and the stomachs of a considerable number at postmortem examination contained quantities of altered blood.

TABLE 1.—*Normal Values for Nonprotein Nitrogenous Constituents of Blood*

	Non-protein Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen	Creatinine	Uric Acid	Rest Nitrogen
Animals on regular diet:						
Number of animals.....	17	13	14	9	14	12*
Number of observations....	17	13	14	9	14	12*
Maximum mg. per cent.....	54.0	21.9	9.3	1.96	1.80	33.5
Minimum mg. per cent.....	31.4	9.0	4.8	1.33	0.10	11.3
Average mg. per cent.....	40.7	15.5	8.12	1.54	0.82	18.0
Nitrogen as per cent total nitrogen:						
Number of animals.....	11	11	9	6	10
Number of observations....	13	13	9	6	12
Maximum per cent.....	50.0	26.7	1.68	1.24	63.7
Minimum per cent.....	26.4	9.8	1.15	0.31	34.6
Average per cent.....	36.8	19.5	1.38	0.53	43.0
Animals on special diet:						
Number of animals.....	16	8	12	2	6*
Number of observations....	20	9	16	2	10*
Maximum mg. per cent.....	52.5	19.7	9.0	2.0	0.8
Minimum mg. per cent.....	25.0	9.8	5.0	0.80	7.3
Average mg. per cent.....	35.6	13.2	7.0	1.90	12.2
Nitrogen as per cent total nitrogen:						
Number of animals.....	8	10	6
Number of observations....	9	14	10
Maximum per cent.....	51.8	25.8	43.4
Minimum per cent.....	31.8	10	35.7
Average per cent.....	41.5	19.6	35.3

* Where creatinine and uric acid had not been determined an average value was assumed for calculation of the rest nitrogen.

BLOOD STUDIES

A. Normal Animals.—Figures for the nonprotein nitrogenous constituents in the blood of normal monkeys are presented in table 1. The figures have been divided into two groups, those from animals on the regular diet, and those from animals fed on the special diet. All monkeys in the latter group had received the special diets for from five days to two weeks previous to the taking of blood. The most striking difference between the two groups is the higher average level of nitrogenous constituents in the blood of animals on the regular diet. This difference is quite inexplicable as there is reason to believe that the special diets contained more nitrogen than the regular diet. The blood samples in both groups were taken in some cases before feeding and

in others, after feeding. In both groups, the average nonprotein nitrogen is higher than it is usually found to be in normal human blood.

The higher uric acid values observed on the special diet cannot be considered significant since only two animals are included in this group. The relative amounts of urea nitrogen, amino-acid nitrogen and creatinine are in accord with those found in human blood.

Ammonia nitrogen was determined in the blood of two monkeys, and only a trace could be found. The variation between maximum and minimum figures for all the nitrogen constituents was quite large, and there seemed to be no difference between the two groups in this respect.

TABLE 2.—*Values for Nonprotein Nitrogenous Constituents of Blood in the Final States of Yellow Fever*

	Nonprotein Nitrogen	Urea Nitrogen	Amino-Acid Nitrogen	Creatinine	Uric Acid	Rest Nitrogen
Animals on regular diet:						
Number of animals.....	26	19	22	6	9	19*
Number of observations.....	33	26	29	6	9	24*
Maximum mg. per cent.....	128.0	46.5	43.7	2.6	1.5	54.6
Minimum mg. per cent.....	44.7	10.7	5.5	1.1	0.5	14.8
Average mg. per cent.....	78.3	27.0	20.9	1.7	0.8	32.2
Nitrogen as per cent total nitrogen:						
Number of animals.....	16	15	5	5	15*
Number of observations.....	23	22	5	5	22*
Maximum per cent.....	47.8	42.2	1.2	0.4	65.4
Minimum per cent.....	14.8	8.1	0.6	0.2	24.7
Average per cent.....	35.7	26.6	0.8	0.6	39.1
Animals on special diet:						
Number of animals.....	5	7	5	2	3	4*
Number of observations.....	8	10	7	2	3	7*
Maximum mg. per cent.....	99.0	28.0	32.7	3.0	1.0	60.0
Minimum mg. per cent.....	50.0	5.3	12.0	2.3	0.5	19.0
Average mg. per cent.....	68.6	16.0	20.8	2.0	0.7	29.6
Nitrogen as per cent total nitrogen:						
Number of animals.....	4	4	2	...	4*
Number of observations.....	6	6	2	...	6*
Maximum per cent.....	56.0	47.2	2.1	...	61.6
Minimum per cent.....	5.3	22.0	1.3	...	20.0
Average per cent.....	23.4	29.5	1.7	...	44.7

* Where creatinine and uric acid had not been determined an average value was assumed for calculation of the rest nitrogen.

B. Analyses of Blood During the Terminal Stages of Yellow Fever.

—The results of blood analyses during the terminal stage of yellow fever are presented in table 2. The figures were obtained only from animals that were moribund or obviously very ill. Some of the animals were in the first day of fever while others had undergone a prolonged febrile period. As has been pointed out previously, the duration of the illness is quite variable, and many monkeys are prostrated and die shortly after the onset of fever. It is only after the disease has produced obvious clinical symptoms that the concentrations of the nitrogenous constituents of the blood are appreciably altered. Figures obtained during the earlier stages of the disease have been collected in another table.

Table 2 shows clearly the great increase in nonprotein nitrogen which occurs in these moribund animals. Coincident with this, there is an elevation of the urea nitrogen and amino-acid nitrogen. Creatinine increases but little and uric acid not at all. The proportion of the total nonprotein nitrogen contributed by these two constituents is greatly reduced.

Calculated as per cent of the total nonprotein nitrogen, the urea nitrogen, although increased on the average in absolute amount, shows a decrease from 41.5 to 23.4 per cent in the special diet group and from 36.8 to 35.7 per cent in the regular diet group.

The most significant change occurs in the amino-acid nitrogen which shows strikingly large gains both in absolute amount and in relation to the total nitrogen. From approximately 19.5 per cent of the total nitrogen in both normal groups it has risen to 26.6 and 29.5 per cent. In one monkey on a special diet it formed 47.2 per cent of the non-protein nitrogen, while another on regular diet showed an absolute value of 43.7 mg. per cent. In only one instance was amino-acid found within the normal range, 5.5 mg. per hundred cubic centimeters. The average increase in both groups is from two and a half to more than three times the normal values.

The absolute concentration of rest nitrogen in both groups is markedly increased, although it does not always form a larger proportion of the total nonprotein nitrogen.

Ammonia nitrogen in both samples of blood from animal no. 8 (table 3) was less than 0.5 mg. per hundred cubic centimeters. Here again can be seen the lower concentration of the constituents in the blood of the animals fed on the special diet.

The notable features of the blood nitrogen at the terminal stage of yellow fever are: (1) high concentration of nonprotein nitrogen; (2) absolute increase in urea concentration which is small in proportion to that of nonprotein nitrogen; (3) an increase of amino-acid nitrogen that is large in proportion to that of nonprotein nitrogen; (4) an increase of rest nitrogen, and (5) the fact that uric acid concentration remains unchanged.

NITROGENOUS CONSTITUENTS OF BLOOD IN THE EARLY STAGES COMPARED WITH THOSE IN THE TERMINAL STAGES OF YELLOW FEVER

In table 3 are presented the results of blood analyses made at intervals during the course of the disease. Two or more blood samples were taken from eight of the animals. The other first samples were drawn during the illness, but before the animals became prostrate, while the last blood was taken either post mortem or when the monkeys were obviously moribund.

TABLE 3.—*The Changes in Blood Nonprotein Nitrogen During the Course of Yellow Fever **

Mon- key Num- ber	Blood Sam- ples	Nonprotein Nitrogen as Mg. per Cent			Nonprotein Nitrogen as per Cent Total Nitrogen			Date	Time	Comment
		Total	Urea	Amino- Acids	Urea	Amino- Acids	Blood Sugar			
2	A	37	12	7	33	20	34	May 29	11:30 a. m.	Second day of fever
	B	78	28	18	36	28	18	May 29	8:30 p. m.	Died during removal of blood
3	A	47	21	6	44	12	...	June 4	Normal
	B	43	20	5	46	12	...	June 8	10:20 a. m.	First day of fever;
4	A	45	17	12	37	28	43	Dec. 8	3:00 p. m.	Conscious, but weak
	B	60	21	19	35	32	...	Dec. 8	7:10 p. m.	10 minutes after death
5	A	60	20	14	33	23	86	Dec. 10	10:00 a. m.	After one day of fever;
	B	128	41	43	32	38	34	Dec. 11	9:00 a. m.	vigorous Died during removal of blood
6	A	36	12	8	32	21	102	Dec. 11	9:30 a. m.	After one day of fever;
	B	83	29	25	35	29	41	Dec. 15	10:20 a. m.	not ill After two days of fever;
	C	88	33	31	38	35	...	Dec. 15	11:20 a. m.	not prostrated Five minutes after death
7	A	47	11	16	23	35	...	Dec. 17	4:20 p. m.	After two days of fever;
	B	57	14	23	25	41	...	Dec. 17	7:30 p. m.	very ill, but not prostrated Five minutes after death
8	A	112	46	27	41	24	...	Jan. 6	10:00 a. m.	Starved for 13 days
	B	119	47	32	39	27	...	Jan. 6	11:00 a. m.	Five minutes after death
M2	A	29	13	8	45	27	...	Nov. 24	9:00 a. m.	After one day of fever;
	B	55	9	27	16	48	...	Nov. 27	8:00 a. m.	bright and lively After three days of fever;
	C	67	11	29	16	43	...	Nov. 27	10:30 a. m.	prostrate Five minutes after death
M3	A	43	20	8	46	18	109	May 2	2:00 p. m.	Appears normal; last meal at 9:30 a. m.
	B	61	17	15	28	25	68	May 3	8:10 a. m.	Drowsy, but vigorous;
	C	67	15	17	22	25	113	May 3	4:10 p. m.	last meal May 2 at 4:30 p. m. Lying down, weak and listless; last meal at 9:10 a. m.
M4	A	24	10	5	42	21	...	May 3	10:15 p. m.	Ten minutes after death
	B	50	28	12	56	24	...	Nov. 2	Normal
M5	..	66	18	15	27	23	...	Nov. 5	11:15 p. m.	Ten minutes after death
9	..	28	10	8	36	30	...	Sept. 30	6:30 a. m.	Fifteen minutes after death
10	..	31	13	7	40	22	...	Feb. 10	9:00 a. m.	After two days' fever; not definitely ill, recovered
11	..	37	..	7	..	19	...	Feb. 11	10:15 a. m.	After two days' fever; not definitely ill, recovered
11	..	37	..	7	..	19	127	Aug. 22	10:15 a. m.	First day of fever; lively, animal killed

* Sample A from no. 3 was taken before the animal was infected. In numbers 9, 10 and 11 the blood was taken during the febrile period, but before clinical symptoms were evident.

Consideration of the blood sugar values obtained during fasting has been included in the remarks wherever the determinations were made. It is interesting to note the extremely low values for blood sugar obtained from the animals in a moribund condition.

The figures given for monkeys 2, 4, 5, 6, M2 and 7 indicate clearly the magnitude of the changes which occur in the last few hours of life.

The percentage of total nitrogen formed by the urea nitrogen and amino-acid nitrogen, respectively, show definitely that these two products do not increase at comparable rates. In the three animals 4, 5 and 8, the urea nitrogen, while increasing in absolute amount, decreases as the per cent of total nonprotein nitrogen in the time intervening

TABLE 4.—*Postmortem Changes in Some Nonprotein Nitrogenous Constituents of Blood*

Num- ber	Minutes Post Mortem	Non- protein Nitro- gen, Mg., per Cent	Urea Nitro- gen, Mg., per Cent	Amino- Acid Nitrogen Mg., per Cent	Urie Acid, Mg., per Cent	Comment
		36.5	9.28	Taken from right basilic vein at 2:20 p. m.
		37.0	9.10	Taken from right heart at 2:25 p. m.
		Animal killed by blow on neck at 2:30 p. m.
	15	40.0	11.15	Taken from right heart at 2:45 p. m.
M6		98.5	51.0	7.6	0.53	Taken from left heart at 2:35 p. m.
	5	100.0	7.9	0.52	Animal killed by blow on neck at 2:38 p. m.
		Taken from left heart at 2:43 p. m. (heart beating)
	14	98.5	49.0	8.5	0.57	Taken from left heart at 2:52 p. m.
		44.1	17.4	8.5	0.45	Taken from right heart at 8:33 a. m.
		Animal killed by blow on neck at 8:34 a. m.
	5	46.2	17.6	10.1	1.05	Taken from left heart at 8:41 a. m.
	15	50.0	11.6	2.50	Taken from left and right heart at 8:49 a. m.
M7		72.3	39.7	8.7	1.25	Taken from right heart at 8:25 a. m.
		Animal killed by blow on neck at 8:28 a. m.
	6	71.0	36.4	9.3	1.57	Taken from left heart at 8:34 a. m.
	14	71.5	36.4	10.1	1.76	Taken from left heart at 8:42 a. m.

between the two analyses. Both absolute and relative concentrations of amino-acid nitrogen, on the other hand, always increase greatly.

Values given for blood samples 2A, 3B, M2A, 6A, 9, 10 and 11, though obtained from monkeys during the febrile period (in the case of 2A just nine hours before death), lie within the normal range.

Postmortem Changes in Some Nitrogenous Constituents of Blood.—Since many of the terminal blood samples were taken a few minutes post mortem, the question arose if part, at least, of the change observed in the nitrogenous metabolites was not a postmortem change.

In these experiments monkeys which had not been infected were used. Blood was analyzed immediately before death and at intervals up to fifteen minutes after death. The animals were killed in a way that would least affect the blood concentration.

The series of analyses recorded in table 4 indicates that there is in some cases an increase in nonprotein nitrogen in the blood which

remains in the animal from five to fifteen minutes after death. At the same time, the amino-acid nitrogen increased by 3.1 mg. and the uric acid by the usually large figure of 2.05 mg. or almost 0.7 mg. of nitrogen. The nonprotein nitrogen did not always increase, but amino-acid nitrogen and uric acid invariably rose slightly. Urea, on the other hand, decreased somewhat.

Part of these differences may be due to analytical error or incomplete mixing of the blood samples as taken from the heart; but the consistent positive tendency shown by most of them indicates undoubtedly that appreciable autolysis has already occurred. However, it was felt that the differences were negligible when compared with the large increases noted in the animals dying of yellow fever.

Monkeys M6 and M7 had both received injections of uric acid in connection with other experiments; M6 six days previously and M7 nine days previously. We have noticed a marked fall of nitrogen excretion after intravenous or subcutaneous injection of uric acid. In some cases the monkeys become practically anuric for a day afterward, and urinary nitrogen returns to the normal level only after five or six days. This nitrogen retention would account for the high concentration in the blood of M6 and M7.

COMMENT

The most consistent pathologic changes in yellow fever are seen in the liver; the kidneys show degenerative changes in a less marked degree; minor alterations are found in the heart and the spleen. Because the liver presents the gravest lesions, amounting, in the most severe cases, to almost complete destruction of the parenchyma of the organ, one would expect changes in metabolism similar to those found after hepatectomy, namely, a loss of ability to deaminize and to form urea, deficient destruction of uric acid and impairment of hepatic glycogen formation.

A study of carbohydrate metabolism during the disease will be published separately. The results of experiments on uric acid reported in this and the succeeding paper have been supplemented by a more complete investigation which will also be presented separately.

In yellow fever no significant change was found in the uric acid concentration of the blood (tables 1 and 2). This is strangely at variance with the results of Mann and his associates,²⁶ who reported definite rises of uric acid in the blood of the dog within a few minutes after complete hepatectomy. In the rabbit McMaster and Drury²⁷

26. Mann, F. C.: Modified Physiologic Processes Following Total Removal of Liver, *J. A. M. A.* **85**:1472 (Nov. 7) 1925. Bollman, J. L.; Mann, F. C., and Magath, T. B.: *Am. J. Physiol.* **72**:629, 1925.

27. McMaster, P. D., and Drury, D. R.: *J. Exper. Med.* **49**:745, 1929.

have observed similar increases after the removal of 80 per cent of the liver. Mann found that blood uric acid in the dog increased roughly in proportion to the extent of liver destruction and was affected long before disturbances of urea formation or hypoglycemia appeared. In yellow fever, monkeys that died with blood sugars as low as from 14 to 28 mg. per hundred cubic centimeters had only traces, or at the most 1 mg. of uric acid per hundred cubic centimeters of blood. Either uricolysis in the monkey is not so easily disturbed as it is in the dog or the rabbit, or it is a function which is not confined entirely to the liver. That species differences with respect to uricolysis exist is suggested by Rabinowitch's²⁸ recent report on a case of acute yellow atrophy. This patient exhibited complete absence of deaminizing powers and extreme hypoglycemia without hyperuricacidemia.

Ergothioneine determinations on the blood of three normal monkeys and three monkeys having yellow fever gave entirely negative results. No red color developed on the addition of the tenth-normal sodium hydroxide and no purplish precipitate appeared even after several hours' standing. Furthermore, the blood of two of the normal monkeys, analyzed by Folin's direct method, was found to contain the equivalent of only 0.89 and 0.63 mg. per cent of uric acid, respectively. One of the animals had received the special diet no. 3; the remainder received the regular diet.

Blood creatinine is slightly increased during the terminal stage of yellow fever (tables 1 and 2), probably as a result of the anuria which frequently occurs shortly before death. The increases are not, however, of the magnitude that one would expect if renal insufficiency was an important feature in the course of the disease.

Only traces of ammonia nitrogen were present in the blood of normal monkeys. In the blood of monkey 1 (A and B, table 3) 0.5 mg. per hundred cubic centimeters and in the bloods of two other animals only traces were found in the premortal stages of the disease.

Alterations in the amounts and proportions of the urea and amino-acid nitrogen fractions of the blood in yellow fever are suggestive of loss of liver function. These changes, however, appear only as a terminal event. On the average in the last stages of the disease, urea nitrogen made up a smaller proportion and amino-acid nitrogen a larger proportion of the nonprotein nitrogen than normal (tables 1 and 2).

Blood amino-acid nitrogen increased to a remarkable degree not only in relation to total nonprotein nitrogen, but also in absolute amount. In only one case was it found within normal limits in an animal that had died of yellow fever. On the other hand, the changes in blood urea nitrogen were less consistent. In a large proportion of the cases it

28. Rabinowitch, I. M.: *J. Biol. Chem.* 83:333, 1929.

actually increased, although the increases were small in comparison with those of total nonprotein and amino-acid nitrogen. In many instances it remained within normal limits. In a few cases it diminished absolutely. In M2 (table 3) there was a definite decrease in blood urea, and in M3 an even more striking loss. In the latter case the disappearance of urea from the blood, which occurred between 4:10 p. m. and post mortem, cannot be accounted for by excretion in the urine, since no urine was passed after 3 p. m. and none was found in the bladder at autopsy. Bollman, Mann and Magath,²⁹ in their hepatectomized dogs, in a few instances recorded appreciable reductions of blood urea nitrogen. Rabinowitch²⁸ found no urea in the blood of a patient with acute yellow atrophy, although only a negligible amount was recovered in the urine. This loss is quite unaccountable, if urea is at all times evenly distributed throughout the tissues, unless it can be utilized or destroyed in some manner by the organism.

The rest nitrogen increased considerably in absolute amount, but not always in proportion to the total nonprotein nitrogen. In animals fed on the regular diet, the average rest nitrogen made up a larger percentage of the total nonprotein nitrogen during the control than it did in the yellow fever period (tables 1 and 2), while in animals receiving special diets the reverse was true.

On the whole then, the blood nonprotein nitrogen and its various components appear to suffer little change during the course of the disease until the premortal period. At this time the observed changes are consistent with, but not entirely characteristic of, the picture which is recognized as the result of total or subtotal ablation of liver function. The complete absence of hyperuricacidemia is out of keeping with the results of experimental investigations on dogs and rabbits. However, as has been pointed out, in at least one human being with maximum liver destruction, blood uric acid was found normal. Species variations in the mode of utilization (and, presumably, oxidation) of purine end-products have long been recognized. Although in its normally low excretion of uric acid the monkey appears more nearly akin to dog than man, in the site of uricolysis he may resemble more closely the human being.

The results of these investigations do not permit the conclusion that the power to form urea from amino-acids invariably suffers; they suggest that in most instances it is greatly impaired before death and in some, completely destroyed. As it seems to be well established that in all animals thus far investigated (dog, rabbit and man) this function is peculiarly confined to the liver, it appears justifiable to conclude that

29. Bollman, J. L.; Mann, F. C., and Magath, T. B.: *Am. J. Physiol.* **78**:258, 1926.

this organ suffers extreme functional injury in yellow fever and that this injury is responsible for the most important disturbances of the blood nonprotein nitrogen.

The rapid terminal rise of blood nonprotein nitrogen and most of its components may be, and probably is, referable to failure of renal function. It is less certain that this failure can be attributed to any specific pathologic changes in the kidneys. It was most striking in animals that developed complete or almost complete anuria, a not uncommon occurrence during the last day of life. The decrease in both urine volume and excretion of nitrogenous metabolites may well have been associated with a fall of blood pressure which usually preceded death. The blood pressure of the normal *Macacus rhesus*, measured directly by inserting a needle connected to a special manometer into the femoral artery, is approximately 120 mm. of mercury, systolic; 60 mm. of mercury, diastolic. In three monkeys, in the prostration characteristic of the last stages of yellow fever, systolic pressures were found to lie between 50 and 60 mm., diastolic between 40 and 50. This low blood pressure often made it difficult to secure blood from moribund monkeys.

SUMMARY

Determinations of total nonprotein nitrogen and the individual nonprotein nitrogenous components (urea, amino-acid, ammonia, uric acid and creatinine) have been made on the blood of normal *Macacus rhesus* monkeys and similar animals with experimentally produced yellow fever.

Uric acid, creatinine, rest nitrogen and ammonia are not constantly altered, although creatinine and rest nitrogen usually rise to a variable extent in the terminal stages of the disease.

The constituents which are chiefly affected are urea and amino-acids. Amino-acid nitrogen rises rapidly in the terminal stages of the disease; urea nitrogen may rise, but sometimes remains constant or falls. In any case amino-acid increases proportionately far more and urea far less than total nonprotein nitrogen, evidence that the power of the liver to deaminate amino-acids and to produce urea is greatly impaired or destroyed. This functional derangement becomes apparent only during the last hours of life.

FATAL HUMAN ANAPHYLACTIC SHOCK

REPORT OF A CASE, WITH AUTOPSY OBSERVATIONS AND REVIEW OF
THE LITERATURE *

JESSE G. M. BULLOWA, M.D.

AND

MENDEL JACOBI, M.D.

NEW YORK

Complications following serum therapy are relatively uncommon. Still more uncommon are reported fatalities. Park¹ estimated that such fatal reactions occur once in 70,000 cases.

Of the pathologic anatomy in cases of fatal anaphylactic shock, little has appeared in the literature. Lamson,² in 1924, was able to collect forty cases of sudden death following the injection of serum; twelve of these cases came to autopsy. Since then, one additional case with necropsy observations has been published. Recently a case in the service of one of us (J. G. M. B.) ended fatally; at necropsy changes were presented so similar to those found in experimental anaphylactic shock as to be worth recording.

REPORT OF CASE

History.—C. S., aged 8, was first admitted to the Willard Parker Hospital on Oct. 4, 1928, with a history of cough, "running nose and eyes," and some fever for one week. On admission, she had a marked conjunctivitis, definite Koplik spots on the buccal mucosae and at the junction of the hard and soft palate, a mucopurulent nasal discharge and a few maculopapules on her face. Schick and Dick tests performed in the admitting room were negative. Within twelve hours after admission, a marked pruritic urticarial eruption developed on her chin, wrists, abdomen and left foot, which disappeared shortly after epinephrine had been administered. On October 6, a generalized maculopapular rash developed on her face and trunk, which faded in four days. She was discharged on October 13 as recovered from her attack of measles.

She was again admitted to the hospital on November 1, with a history of general malaise, some fever and sore throat which had lasted four days. On admission, she appeared moderately toxic. Considerable mucopurulent discharge was present from the left nostril. A small piece of grumous, greenish membrane

* Submitted for publication, Dec. 24, 1929.

* From the medical and pathological services of the Willard Parker Hospital for Contagious Diseases, New York, and the pathologic laboratory of the Brownsville-East New York Hospital, Brooklyn.

1. Park, W. H.: Tr. A. Am. Phys. **28**:95, 1913; Antitoxin in Diphtheria, J. A. M. A. **76**:109 (Jan. 8) 1921.

2. Lamson, R. W.: Sudden Death Associated with Injection of Foreign Substance, J. A. M. A. **82**:1096 (April 5) 1924.

was present beneath the left inferior turbinate and on the left tonsil. There was moderate edema of the neck. The pharynx was somewhat reddened and granular. The heart sounds showed the first sound to be of poor quality. The scratch skin test for horse serum sensitivity showed no reaction in a few minutes.

The patient was given 5,000 units of diphtheria antitoxin intravenously. She was turned on her side preparatory to receiving an additional intramuscular injection of antitoxin. She complained of being nauseated, and began to vomit. The most marked feature was the very great inspiratory effort in which all the accessory muscles participated, apparently without expansion of the chest, as if a foreign body were present. The chest continued to be small in spite of the obvious expansion of the free border of the ribs and the tugging of the sternomastoids. On auscultation, very little air was heard to enter the chest. The facial muscles were contracted. The contorted face betokened terror.

Epinephrine was given intravenously. Laryngoscopy and bronchoscopy were performed. The trachea was seen to be narrow. Oxygen was administered through the bronchoscope, but very little air seemed to enter the lung. Mouth to mouth insufflation was employed with the hope of increasing the carbon dioxide content and therefore the depths of the inspirations and possible ultimate relaxation of the musculature. Atropine was administered. Gradually, the heart became more irregular, and finally ceased to beat. Respirations became more and more apneustic, later with prolonged expiration, finally gasping, until they ceased several minutes before the heart had stopped.

Autopsy.—Autopsy was performed seven hours postmortem by one of us (M. J.). The body was that of a well developed and nourished white girl whose upper and lower extremities especially were mottled with fine and larger dull, crimson-bluish areas separated by pallid white blotches. The abdomen and face were quite pallid; the buttocks, back and shoulders showed large, blotchy livid areas. The vessels of the dura, sinuses and brain surface were markedly distended with dark, fluid blood. The jugular veins were similarly markedly distended with large amounts of fluid blood. The abdominal veins, notably the portal, both renals and the inferior vena cava were only moderately filled with fluid blood; the mesenteric, splenic and iliac veins were prominent but not unusually distended. No thrombi were found in any vessel.

The turbinates, the nasal septum and nasopharynx were covered by patches of dirty grayish green, blood-tinged exudate confluent over the nasopharynx into a distinct membrane. Beneath this firmly adherent exudate, the mucosa was a deep red, dull and ulcerated; the intervening mucosa was markedly reddened and dulled. On the left tonsil were shreds of firmly adherent fibrinonecrotic, blood-tinged exudate.

When the chest was opened, the heart was seen to be tremendously increased in size. The parietal pericardium, transparent and glistening, was tightly stretched over it; the pericardial sac contained no fluid. The right auricle was distended to about three times, and the right ventricle, to about twice its usual size. Each was filled with dark fluid blood. The left auricle and ventricle were firm-walled, collapsed and empty. The left ventricular myocardium was firm, its papillary muscle contracted; that of the right ventricle was thin and toneless, its papillary muscle flabby. The valves and endocardium were normal.

The heart weighed 97 Gm. The thickness of left and right ventricle, respectively, without the papillary muscle, was 1.6 and 0.1 cm. The left auricle was 0.3 cm. thick; the right auricle less than 0.1 cm., and very transparent. The diameter of the left ventricle was about 2.8 cm.; the right ventricle, about 7.7 cm.; the left auricle, about 3.4 cm. and of the right auricle about 8.9 cm.

The lungs were moderately emphysematous and diffusely reddened. They could be cut only with some difficulty, the parenchyma, crackling and rebounding under the knife. On section, the cut surface was dry. Bronchioles could be seen only with difficulty and only in very few places.

The liver weighed 1,100 Gm. It showed no gross lobulation, the cut surface being diffusely brown and dulled. The spleen weighed 72 Gm. Its capsule was tense, its consistency soft; on section, the cut surface was mushy, semisolid and of a dull beet-red color in which neither corpuscles nor trabeculae could be distinguished.

Microscopic Examination.—All the alveoli were widely distended and empty, and the alveolar walls were thin and ruptured in places. The bronchiolar epithelium was arranged evenly in deep folds around the entire circumference; the whole layer was separated from the underlying wall by a narrow, clear zone. The bronchiolar lumina were quite narrowed. The arteriolar walls were thickened, their elastic layers markedly folded, their lumina narrow, empty, and in places nearly obliterated where the arteriolar walls were in apposition. An occasional rather large arterial vessel appeared widely dilated and filled with a compact mass of well preserved erythrocytes. Such vessels showed their elastic layers without any folds, and circular throughout. Many other large vessels (without definite elastic layer and presumably venous in character) were irregular in outline; their lumina were distinct and entirely empty.

The lobules of the liver were indistinctly outlined by a few narrow sinusoids containing a few erythrocytes in the extreme periphery of the lobule. In places there appeared a small central vein, quite round, and entirely filled with masses of red cells. Elsewhere throughout the section, no distinct sinusoids were distinguishable, or they appeared as narrow, empty, irregular spaces. The hepatic cells were large, contiguous but nowhere in the form of regular cords, the cells forming a very irregular network. The cellular cytoplasm was coarsely granular, pale acidophilic, and devoid of glycogen. The nuclei were small and deeply and homogeneously basophilic. No changes were noted in the occasional Kupffer cell seen. In the portal spaces, the arterial radicles were narrow, thick-walled, and frequently without discernible lumen, while the venous branches were large, round and filled with erythrocytes.

The spleen showed a distinct congestion of the sinuses and a moderate edema of the corpuscles, most of which contained nests of concentric epithelioid cells which in places were entirely necrotic.

The kidneys, brain cortex and suprarenals showed a pronounced congestion of their capillaries.

Bacteriologic Examination.—The antemortem nasal cultures were negative for Klebs-Loeffler bacilli but postmortem cultures were positive. Antemortem pharyngeal culture was positive for Klebs-Loeffler bacilli.

REVIEW OF LITERATURE

Klotz³ reported the case of a 2 year old child who did not have a history of asthma, and who had had no injections of foreign protein previously. Intramuscular injection of 1.2 cc. of diphtheria antitoxin produced death in ten minutes. At autopsy, the thymus was found "enlarged."

3. Klotz, O.: Montreal M. J. **36**:615, 1907.

Kortright ⁴ reported the case of a 16 year old girl who gave no history of asthma or urticaria, and who had had no previous injection of foreign protein. Five minutes after the intramuscular injection of 10 cc. of diphtheria antitoxin, she developed generalized tingling sensation and a sense of a lump in her stomach; she became quite restless, and developed tonic, then clonic, convulsions and opisthotonos. She became cyanotic and died, apparently from respiratory failure; the heart continued to beat for three minutes after respiration had ceased. The entire process from onset of symptoms until death occurred lasted eight minutes. At autopsy, marked congestion of the brain, kidneys and liver was noted.

Gillette ⁵ had a 52 year old patient with a history of asthma but no previous injection of foreign protein, who was given 2,000 units of diphtheria antitoxin intramuscularly for the asthma. Shortly after the injection, a prickling sensation developed in the chest and neck, and the patient died five minutes after the onset of symptoms, death being preceded by a tonic spasm. Autopsy showed the lungs larger and more voluminous than normal. Status lymphaticus was suggested by the body configuration. The heart was empty and weighed 360 Gm. The spleen was congested; the liver was noted as normal.

Collier and Dreyer ⁶ recorded the case of an 18 year old girl who had some time (not noted) previously been given a prophylactic dose of diphtheria antitoxin for suspected diphtheria. She had no other history of a previous injection of foreign protein, but had asthma for which an unrecorded amount of diphtheria antitoxin was injected intramuscularly. The patient fell from her chair, dying within a few minutes. Note is made at autopsy that the "lungs and heart were in a condition accounted only for by spasm."

Koch ⁷ recorded the case of a 6 year old child with diphtheria and without any history of asthma, urticaria or hay-fever, who had been given 1.2 cc. of diphtheria antitoxin intramuscularly. Fourteen days later, 5 cc. of antistreptococcus serum was given intramuscularly and again five hours later 10 cc. of the serum for a complicating scarlatinal infection. Immediately after the latter injection, the child developed facial twitches, its pupils became dilated, its body cyanosed and its thorax immobile; death ensued within two minutes of the injection. Autopsy revealed a fairly pronounced emphysema of the lungs.

4. Kortright, quoted by Halsted, T. H.: *Am. J. M. Sc.* **130**:863, 1905.

5. Gillette, H. F.: *Diphtheria Antitoxin in Bronchial Asthma*, *J. A. M. A.* **50**:40 (Jan. 4) 1908.

6. London Letter, Sudden Death After the Prophylactic Injection of Diphtheria Antitoxin, *J. A. M. A.* **52**:223 (Jan. 16) 1909.

7. Koch, W.: *Berl. klin. Wchnschr.* **52**:685, 1915.

Gurd's⁸ patient, aged 30, had no history of asthma or previous injection of foreign protein. Five cubic centimeters of tetanus antitoxin given subcutaneously was followed by vomiting in two and one-half hours, after which bloody diarrhea and cyanosis appeared. Death ensued within twenty-four hours. This patient had a history of vomiting and bloody diarrhea five years previously. At autopsy, the lungs were found to be emphysematous and with subpleural "blood collections." Microscopic examination showed alveolar rupture. The bronchioles were contracted and contained red blood cells. The arteries were normal, the veins distended with blood. The heart was noted of normal size and shape, the right ventricle filled with fluid blood and clots and presenting a few subpericardial petechiae. There was a moderate dilatation of the splanchnic vessels, and the spleen, liver and kidneys were congested. The thymus was completely atrophied. The abdominal lymph nodes were larger than normal.

Waugh⁹ injected 4,000 units of diphtheria antitoxin intramuscularly into a 17 year old patient with diphtheria who had no history of asthma or urticaria, but who had received diphtheria antitoxin ten years previously. At that time she had become cyanotic and dyspneic, had frothed at the mouth and had been "severely ill." Death with similar symptoms followed within ten minutes after the second injection. The short protocol on the necropsy notes a general venous stasis and pulmonary congestion.

Boughton's patient,¹⁰ aged 29, suffering from horse asthma, had had no previous injection of foreign protein. One minim (0.06 cc.) of horse serum (undiluted?) was injected intravenously for desensitization; death followed within forty-five minutes with typical asthmatic symptoms. Ephedrine gave but slight relief. At autopsy, there was an intense injection of all the vessels of the abdomen, especially those of the stomach, mesentery, gallbladder and appendix. The entire small intestine was reddened, the submucous vessels dilated (microscopic). The parietal peritoneum was injected. The lungs were enormously dilated and emphysematous, with a hemorrhagic area 4 cm. in diameter on the lateral surface of the left lower lobe covered by an organizing gelatinous exudate. Microscopic examination revealed interstitial hemorrhages in this area. The peribronchial and arteriolar muscle was "thick." The heart was firm and of normal size, and showed a few subpericardial petechiae on the posterior surface. Microscopically, small hemorrhages into the myocardium were seen; the small vessels of the

8. Gurd; Fraser and Roberts: *Lancet* 1:763, 1920.

9. Waugh, G. H.: *Brit. J. Child. Dis.* 15:97, 1918.

10. Boughton, T. H.: *Anaphylactic Death in Asthmatics*, *J. A. M. A.* 73: 1912 (Dec. 27) 1919.

myocardium were apparently thickened. The spleen presented a number of small, reddish-brown bullae 1 mm. in diameter along the anterior border. Microscopically, the kidneys showed interstitial hemorrhages and marked hyperemia; the suprarenals showed hyperemia and contained microscopic hemorrhages. The liver showed edema and "thickened artery walls."

MacCallum¹¹ reported the case of an 8 year old patient without any previous history of asthma or injection of foreign protein, who within two minutes after receiving 2,000 units of diphtheria antitoxin subcutaneously as a prophylactic measure complained that "it had gone to her stomach." She rapidly became cyanotic, experienced a choking sensation, went into a collapse, and died in five minutes from the time of injection. Autopsy revealed a contracted left ventricle and a flaccid right ventricle filled with dark fluid blood. The mesenteric lymph nodes were caseous. In the stomach was about one-half pint of undigested food (bacon, bread, butter and tea) taken one and one-half hours before the injection.

Dean's patient,¹² aged 22, without any history of asthma or previous injections of foreign protein, had received tetanus antitoxin. Thirteen days later, he received another dose of 500 units of the antitoxin subcutaneously, after which he began to vomit, suddenly became cyanotic, and died within seventy minutes of the injection. Autopsy showed an increased amount of lymphoid tissue in the neck and mediastinum. The liver sinuses (microscopically) were dilated and engorged.

Lamson² reported two personal cases. The first patient, aged 17, who had asthma but had had no previous injection of foreign protein, received 750 units of diphtheria antitoxin intramuscularly and died within ten minutes. Autopsy notes recorded only an enlarged thymus.

The second patient, also 17 years of age, without any previous history of asthma or injection of foreign protein, received 500 units of diphtheria antitoxin intramuscularly; he became cyanotic rapidly thereafter, then comatose, developing a marked frothy fluid in the nose and pronounced pulmonary edema ("fluid in lung?"). Death occurred ten minutes from the time of the injection. Autopsy notes stated that the lungs were voluminous and contained a small amount of frothy fluid, and that the thymus was distinctly enlarged.

Mendeloff¹³ reported the case of a man who died within a few minutes after the injection of antimeningococcus serum. Necropsy showed

11. MacCallum, A. D.: *Brit. M. J.* 2:596, 1919.

12. Dean, H. R.: *J. Path. & Bact.* 25:305, 1922.

13. Mendeloff: *Fatal Anaphylaxis Following Intravenous Injection of Antimeningococcic Serum*, *J. A. M. A.* 82:1862 (June 7) 1924.

a purulent meningitis and an enlarged thymus. No reference was made to the state of the heart, lungs or vessels, and the author (personal communication) recalled no notation of the state of these organs.

EXPERIMENTAL WORK

Arthur ¹⁴ noted a marked drop in blood pressure to zero in a few minutes in instances of anaphylactic shock in rabbits. The chest, opened immediately post mortem, showed the ventricles in systole, the auricles contracting feebly and infrequently. Similar observations were made by Friedberger ¹⁵ and Scott, ¹⁶ who also noted an extreme congestion of the portal system.

Caesaris-Demel ¹⁷ found increased tonus and decreased amplitude of each heart beat of the isolated heart of a sensitized animal perfused with Locke's solution to which the sensitizing protein had been added. No stoppage of the heart was noted. Auer, ¹⁸ by direct observation of the thoracic contents during shock, found that the lungs did not collapse as well as normally in the expiratory phase. The heart was slowed, with the right ventricle more distended and tense than usual. Later, small hemorrhages appeared on the surface of the right ventricle, the heart suddenly beat quite slowly, the right auricle did not contract, and the right ventricle filled remarkably and then stopped beating, death ensuing in thirty minutes after injection of the protein. Later, ¹⁹ Auer demonstrated electrocardiographic changes indicative of ventricular damage and heart block.

Airila ²⁰ found the pulmonary arterial pressure rising from 7 to 26 mm. of mercury within thirty seconds after the injection of protein with a coincidental drop in systemic blood pressure, the drop occurring near the peak of the high pulmonic pressure. That this drop apparently is not due to an active abdominal vasodilatation, Shultz ²¹ suggested, the typical systemic blood pressure drop occurring when the entire abdominal area was clamped off before shock was produced. In cats, Edmunds ²² found a rise in pulmonary venous pressure, a peculiar change similarly observed

14. Arthus, M.: *Arch. internat. de physiol.* **7**:471, 1908-1909.

15. Friedberger, E.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **3**:581, 1909.

16. Scott, W. M.: *J. Path. & Bact.* **15**:31, 1911.

17. Caesaris-Demel, A.: *Gior. d. r. Accad. di med. di Torino* **73**:9, 1910.

18. Auer, J.: *J. Exper. Med.* **14**:476, 1911.

19. Auer, J., and Robinson, G. C.: *J. Exper. Med.* **18**:450, 1913.

20. Airila, Y.: *Skandin. Arch. f. Physiol.* **31**:385, 1914.

21. Shultz, W. H., and Jordan, H. E.: *J. Pharmacol. & Exper. Therap.* **2**:375, 1910-1911.

22. Edmunds, C. W.: *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **22**:181, 1914.

by Drinker and Bronfenbrenner.²³ Coca²⁴ found the pulmonary blood bed obstructed in the height of shock.

Manwaring,²⁵ in heart lung preparations of guinea-pigs, found that the flow of very dilute solutions of antigen was stopped if the guinea-pigs had previously been sensitized to it.

Drinker and Bronfenbrenner,²³ whose report is detailed, found that in rabbits in which shock had been produced the pulmonic blood pressure rose within two minutes after the injection of the shock dose, the pressure either began to fall in twenty minutes or remained up for more than two hours. The high pressure may be lowered temporarily by the administration of nitrites. The systemic blood pressure falls and does not return by the end of the experiment. The minute volume of the lungs is increased by an increased respiratory rate, although the respiratory amplitude is lowered. The right auricle and ventricle dilated progressively, death occurring suddenly as in cases of pulmonary embolism or slowly as the result of an inability to maintain the necessary pressure head.

In the cat, an animal sensitized with difficulty, the pulmonary arterial pressure rise is small and well compensated, and the venous pressure falls slightly with the fall in systemic blood pressure, an occurrence which Weil²⁶ thought indicated a stoppage of circulation by swollen liver cells. In monkeys, a few of which were experimented with, no changes were noted with animals "sensitized" to the blood of guinea-pigs. The authors expressed doubt as to whether sensitization had actually occurred.

COMMENT

The cases reviewed presented clinical manifestations comparable to anaphylactic shock in experimental animals. The postmortem observations, however, showed no marked constancy. Emphysema was seen in six instances, in two of which bronchiolar contraction⁸ and peribronchiolar muscular thickening¹⁰ were noted; in the latter case, arteriolar thickening in the lungs, myocardium and liver likewise were present. In only one case⁸ was the emphysema apparently extreme enough to cause rupture of the alveolar walls and the presence of subpleural collections of blood, while in another¹⁰ interstitial hemorrhages were present. One case¹¹ showed dilatation of the right side of the heart as noted in our case; in one case⁶ "spasm" was recorded; in two²⁷ the postmor-

23. Drinker, and Bronfenbrenner, J.: *J. Immunol.* 9:387, 1924.

24. Coca, A. F.: *J. Immunol.* 4:219, 1919.

25. Manwaring, W. H.: *Intestinal and Hepatic Reactions in Anaphylaxis*. *J. A. M. A.* 77:849 (Sept.) 1921.

26. Weil, R.: *J. Immunol.* 2:525, 1916-1917.

27. Gurd (footnote 8). Boughton (footnote 10).

tem observations were grossly normal, except for a few subpericardial petechiae, and in one¹⁰ microscopic intramyocardial hemorrhages were noted. The liver was congested in four instances;²⁸ in one instance edema of the parenchyma was noted, the only observation similar to that experimentally noted by Weil.²⁶ The spleen was congested in three cases,²⁹ the kidney in three,³⁰ the brain in one case,⁴ the gastro-intestinal tract and peritoneum in one,¹⁰ and the adrenals in one,¹⁰ in which case interstitial adrenal petechiae were present. In one case,⁹ general venous stasis and pulmonary congestion without further details were noted; in one,⁸ moderate splanchnic dilatation. More inconstant were the autopsy observations referable to the thymus and the lymphatic system. In three cases, enlarged thymus was present, in one 2 year old child³ and in two 17 year old patients;¹³ in the latter, voluminous lungs were also noted at autopsy; in the other cases, no additional observations are recorded. One case report⁵ records "status configuration" congested spleen and voluminous lungs. In one case,⁸ atrophic thymus and enlarged abdominal lymph nodes were noted in a 30 year old patient; in this case the previous history of bloody diarrhea and vomiting and the presence of enlarged abdominal nodes suggests the possibility of an old intestinal tuberculosis. One patient,¹² 22 years old, showed an increased amount of lymphoid tissue in the neck and mediastinum. In this group no mention is made of hypoplasia of the heart, vessels or other viscera further than to substantiate the diagnosis of status lymphaticus. It does not seem possible to correlate these observations with the death of the patients.

Nor does there seem to be any correlation between the presence of previous anaphylactic symptoms or injection of foreign protein with the presence of thymic or hyperplastic lymphoid tissue. In the group showing such tissue four patients presented no previous history of asthma, urticaria or hay-fever, nor had they had any previous injection of protein, while two patients had such a history. In the group showing no suggestion of status lymphaticus, four patients gave no previous history and three patients presented such data.

These anatomic observations vary considerably and are incompletely described in many instances. The emphysema and general venous stasis and parenchymal congestion are prominent. In several cases, arteriolar thickening was noted. In our case, we demonstrated thickening of the pulmonary arterioles; the elastic membranes were wrinkled markedly so as to suggest the presence of marked spasm. The extreme dilatation of

28. Kortright (footnote 4). Gurd (footnote 8). Dean (footnote 12). Boughton (footnote 10).

29. Gillette (footnote 5). Gurd (footnote 8). Boughton (footnote 10).

30. Kortright (footnote 4). Gurd (footnote 8). Boughton (footnote 10).

the right side of the heart with general congestion and markedly contracted left side of the heart devoid of fluid contents or blood clots seem further to substantiate the belief that the cause of death in anaphylactic shock is failure of the right side of the heart and inability to maintain pressure in the pulmonary system as the result of obstruction of the arteriolar pulmonary blood bed, as indicated by the experimental work cited.

SUMMARY

1. A case of fatal anaphylactic shock after a single injection of diphtheria antitoxin is reported.

2. The pathologic anatomy is described, consisting chiefly of acute pulmonary emphysema, dilatation of the right side of the heart, general venous stasis and visceral congestion; the left side of the heart is contracted and empty. Microscopically, the changes consist chiefly of thickening of the arteriolar wall, especially in the lungs.

3. These anatomic changes are presented as corroborative morphologic evidence to substantiate the experimental work on the pathogenesis of fatal anaphylactic shock reviewed. This consisted chiefly in overfilling of the lungs, which remained distended, a drop in the peripheral blood pressure with a concomitant rise in the pulmonary arterial pressure, a progressive weakening of cardiac contraction and a slowing and final stopping of the heart, with the right auricle and ventricle in diastole and very much dilated.

4. The cases of anaphylactic shock which came to autopsy are reviewed in detail. Doubt is cast on the rôle of the thymus in such cases.

THE INFLUENCE OF A SPECIAL BREAKFAST ON THE BASAL METABOLISM OF PATIENTS WITH A PATHOLOGIC CONDITION*

CHI CHE WANG, PH.D.

AND

JEAN E. HAWKS, M.S.

CHICAGO

Benedict¹ demonstrated that a special breakfast consisting of 200 cc. of coffee free from caffeine, 16 mg. of saccharin, 30 Gm. of medium cream and 25 Gm. of potato chips had little or no effect on the production of basal heat in normal subjects if the test was made one hour or longer after the meal. However, he did not recommend the use of such a meal without further investigation in cases of patients with a pathologic condition. In view of the practical application of such a breakfast to pathologic cases, the present study was conducted.

DuBois,² in his study of the metabolism of boys between the ages of 12 and 13, also employed a small breakfast consisting of one egg, one slice of toast with butter and a glass of milk. The test was made four hours after the meal. Higgins³ used the same breakfast in his study made on a young man, and found that the production of heat returned to basal value in three and one-half hours after the meal. Later DuBois and his associates⁴ demonstrated that the production of heat in five adults was 2 per cent above their basal value two hours after the ingestion of a meal consisting of one slice of bread, 8 Gm. of butter, 10 Gm. of sucrose and 60 Gm. of milk. Six hours later, the value was slightly below the fasting level. In the study of the basal metabolism of children, Bauer and Blunt⁵ employed a special breakfast with a fuel value varying from 200 to 470 calories, and the protein content from

* Submitted for publication, Dec. 11, 1929.

* From the Nelson Morris Institute for Medical Research of the Michael Reese Hospital, Chicago, aided by the Gusta Morris Rothschild Fund and the S. J. T. Straus Fund.

1. Benedict, C. G., and Benedict, F. G.: A Permissible Breakfast Prior to Basal Metabolism Measurements, Boston M. & S. J. **188**:849 (May) 1923.

2. DuBois, E. F.: Clinical Calorimetry. XII. The Metabolism of Boys 12 and 13 Years Old Compared with the Metabolism at Other Ages, Arch. Int. Med. **17**:887 (June) 1916.

3. Higgins, quoted by DuBois (footnote 2).

4. Soderstrom, G. F.; Barr, D. P., and DuBois, E. F.: Clinical Calorimetry. XXVI. The Effect of a Small Breakfast on Heat Production, Arch. Int. Med. **21**:613 (May) 1918.

5. Bauer, V., and Blunt, K.: Effect of a Small Breakfast on the Energy Metabolism of Children, J. Biol. Chem. **59**:77 (Feb.) 1924.

TABLE 1.—Variation of Basal Heat Production Measured One Hour Apart

Name	Sex	Age	Height, Cm.	Weight, Kg.	Pulse	Tempera- ture	Predicted Calories per 24 Hours H-B	Heat Production						Diagnosis	
								Fasting			Difference				
								First Test		One Hour Later		Calories per 24 Hours	Calories per 24 Hours		Difference
								Calories per 24 Hours	Per Cent Variation from Normal	Calories per 24 Hours	Per Cent Variation from Normal				
L. F.	F	55	154	52.4	71	98.1	1,184	1,634	+42.2	1,645	+38.9	— 39	— 2.3	Thyrototoxicosis	
S. W.	F	38	162	47.0	71	97.2	1,227	1,639	+33.6	1,577	+28.5	— 61	— 3.7	Thyrototoxicosis	
H. W.	M	36	161	51.7	92	97.4	1,339	1,728	+29.1	1,775	+32.6	+ 47	+ 2.7	Thyrototoxicosis	
E. B.	F	53	143	36.6	75	97.4	993	1,132	+13.4	1,111	+11.3	— 21	— 1.9	Decompensated heart	
A. J.	F	43	165	48.0	86	98.2	1,217	1,362	+11.9	1,429	—17.4	+ 67	+ 4.9	Tumor of cecum	
S. A.	M	37	170	58.0	65	97.7	1,350	1,486	+11.7	1,594	+19.9	+103	+ 7.3	Decompensated heart	
D. W.	F	55	159	71.5	66	98.6	1,376	1,536	+11.6	1,378	+ 0.2	—153	—10.3	Thyrototoxicosis	
B. K.	F	29	166	70.8	70	98.6	1,504	1,678	+11.5	1,591	+ 5.1	— 97	— 5.7	Thyrototoxicosis	
R. R.	F	75	154	59.6	77	97.7	1,159	1,292	+11.4	1,286	+10.9	— 6	— 0.4	Carcinoma; thyrototoxicosis; diabetes	
S. W.	F	45	144	56.5	97	98.2	1,247	1,374	+10.2	1,270	+ 1.8	—104	— 7.6	Peptic ulcer; rheumatism	
W. T.	F	23	161	49.6	96	97.8	1,296	1,360	+ 4.9	1,352	+ 4.3	— 8	— 0.6	Thyrototoxicosis	
M. H.	M	29	172	65.8	51	97.4	1,636	1,679	+ 2.6	1,697	+ 3.7	+ 18	+ 1.1	Jaundice	
J. R.	M	23	160	42.5	59	98.2	1,294	1,312	+ 1.4	1,302	+ 0.6	— 10	— 0.8	Spinal meningitis	
M. D.	F	61	148	51.4	71	98.2	1,135	1,149	+ 1.2	1,098	— 3.2	— 51	— 4.4	Cholecystitis	
J. M.	M	21	180	69.0	80	99.0	1,774	1,781	+ 0.4	1,861	+ 4.9	+ 80	+ 4.5	Lymphosarcoma	
J. H.	F	27	166	60.7	80	98.6	1,417	1,461	— 3.9	1,442	+ 1.8	+ 32	+ 6.0	Normal	
S. K.	F	29	156	51.4	90	98.7	1,390	1,237	— 4.8	1,263	— 2.8	+ 26	+ 2.1	Endocarditis	
J. O.	F	22	168	57.5	67	98.4	1,413	1,286	— 9.0	1,370	— 3.0	+ 84	+ 6.5	Normal	
M. S.	M	20	184	73.1	61	97.4	1,358	1,685	— 9.3	1,768	— 4.9	+ 83	+ 4.9	Normal	
D. R.	F	34	163	112.4	66	97.8	1,872	1,635	—12.7	1,622	—13.3	— 13	— 0.8	Obesity and cholecystitis	
Average.....								+ 7.87	+ 7.74	+ 1.35	+ 0.08		

3 to 13.8 Gm. The average consumption of oxygen taken from three and one-half to four hours after the meal was 0.6 per cent above the fasting level.

EXPERIMENTAL WORK

A total of ninety-six experiments were made on a group of three laboratory workers serving as controls and on twenty-two patients of whom twelve were suffering from thyrotoxicosis, three from cardiac disturbances, and the others from diabetes, jaundice, obesity, rheumatic fever, meningitis and cholecystitis. All the precautions for a true basal test were carefully followed, and each patient had had several tests before this investigation was undertaken. A resting period of thirty minutes preceded each test. In the control series, which was conducted on fourteen females and six males, a second test was made one hour after the first, during which interval the patients were allowed to sit up for one-half hour. In addition to the twenty people who served as subjects in the control series, five patients (four males and one female) suffering from thyrotoxicosis were used in the second series. In this series the patients received the special breakfast recommended by Benedict¹ after the basal test, and a second test was made one hour later. The Roth-Benedict⁶ respiration apparatus was employed throughout this investigation, and the results were compared with the Harris-Benedict standards.⁷

RESULTS

In the control series the production of heat for the first test ranged from +42.2 to -12.7 and the second test from +38.9 to -13.3 per cent as compared with the standards. The difference between the two tests varied from +108 to -158 calories per twenty-four hours with a maximum variation of 10.3 and a minimum of 0.4 per cent. The average difference of the two tests was 1.35 calories, or 0.08 per cent. In the second series the percentage variation in the production of heat for the first test ranged between +74.6 and -14.6, while the corresponding values for the test made one hour after the meal were +68.3 and -11.8 per cent as compared with the standards. The difference between the two tests was from +144 to -173 calories per twenty-four hours with a maximum difference of 8.9 and a minimum of 0.5 per cent. The average difference of the two tests was 1.75 calories, or 0.53 per cent. In comparing the two series the difference in the production of heat for the two tests made on normal subjects was smaller in the second series than in the control. The average percentage difference of the control series was +5.8 as compared with +0.7 of the second series. All but one of the six patients suffering from thyrotoxicosis who served as subjects in both series gave a greater percentage difference

6. Roth, P.: Modifications of Apparatus and Improved Technic Adaptable to the Benedict Type of Respiration Apparatus, Boston M. & S. J. **186**:457, 1922.

7. Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Washington, D. C., Carnegie Institution of Washington, 1919, p. 279.

TABLE 2.—Variation in Basal Metabolism One Hour After a Small Breakfast

Name	Sex	Age	Height, Cm.	Weight, Kg.	Pulse	Tempera- ture	Predicted Calories per 24 Hours H-B	Heat Production						Diagnosis
								Fasting		1 Hour After Food		Difference		
								Calories per 24 Hours	Per Cent Variation from Normal	Calories per 24 Hours	Per Cent Variation from Normal	Calories per 24 Hours	Per Cent	
D. M.	M	52	170	57.8	1,360	2,374	+74.6	2,290	+63.3	84	-3.5	Thyrototoxicosis
S. W.	F	38	162	46.9	96	1,225	1,972	+61.0	1,849	+50.1	123	-6.2	Thyrototoxicosis
W. M.	M	33	162	41.7	1,228	1,974	+60.7	1,933	+57.4	41	-2.0	Thyrototoxicosis
S. W.	F	38	162	47.2	84	99.1	1,228	1,913	+47.6	1,933	+41.5	75	-4.1	Thyrototoxicosis
S. B.	M	40	184	78.4	97	97.8	1,773	2,644	+47.4	2,504	+40.0	140	-5.3	Thyrototoxicosis
L. F.	F	55	154	52.7	73	98.6	1,187	1,732	+45.9	1,702	+43.4	30	-1.7	Thyrototoxicosis
N. W.	M	26	162	50.6	92	97.5	1,329	1,835	+28.1	1,805	+35.8	20	-1.6	Thyrototoxicosis
R. R.	F	75	155	53.6	88	1,161	1,569	+33.1	1,645	+41.7	76	+4.8	Thyrototoxicosis; carcinoma; diabetes
K. M.	M	50	166	63.7	1,435	1,933	+34.7	1,760	+22.6	173	-8.9	Thyrototoxicosis
N. W.	M	26	161	49.8	92	98.4	1,313	1,755	+33.7	1,899	+44.6	144	+8.3	Thyrototoxicosis; carcinoma;
R. R.	F	75	154	53.4	83	97.4	1,158	1,496	+29.2	1,574	+35.9	78	+5.2	Thyrototoxicosis; diabetes
D. W.	F	55	159	72.7	90	98.4	1,385	1,750	+26.3	1,723	+24.3	27	-1.5	Thyrototoxicosis
S. A.	M	59	170	57.3	66	97.2	1,320	1,587	+20.2	1,506	+14.1	81	-5.1	Decompensated heart
B. K.	F	29	165	71.2	72	98.0	1,506	1,773	+17.7	1,855	+21.8	62	+3.5	Thyrototoxicosis
A. G.	F	40	145	46.4	1,150	1,352	+14.6	1,374	+16.4	22	+1.6	Thyrototoxicosis
E. B.	F	58	143	37.3	69	98.6	1,006	1,138	+13.1	1,212	+20.5	74	+6.5	Decompensated heart
A. J.	F	43	165	48.5	81	98.4	1,222	1,310	+7.2	1,354	+10.8	44	+3.4	Tumor of cecum
J. R.	M	23	160	41.8	110	97.6	1,286	1,348	+4.8	1,341	+4.3	7	-0.5	Spinal meningitis
Sn. W.	F	45	145	56.2	114	98.3	1,250	1,310	+4.8	1,377	+10.2	67	+5.1	Rheumatic fever; peptic ulcer
M. H.	M	29	172	66.5	52	97.5	1,640	1,696	+3.0	1,793	+8.9	97	+5.7	Jaundice
J. M.	M	21	181	70.3	77	98.6	1,797	1,838	+2.8	1,946	+7.2	88	+4.8	Lymphosarcoma
W. T.	F	28	161	50.0	59	97.7	1,300	1,298	-0.1	1,306	+0.4	8	+0.6	Thyrototoxicosis
M. S.	M	20	184	72.8	63	97.9	1,832	1,834	-1.0	1,834	+0.1	50	+2.7	Normal
M. D.	F	61	148	51.5	72	98.0	1,136	1,116	-1.7	1,104	-2.8	12	-1.1	Cholecystitis
J. H.	F	27	166	61.3	71	98.2	1,421	1,368	-3.7	1,335	-6.1	33	-2.4	Normal
J. C.	F	22	168	56.9	65	98.0	1,407	1,246	-11.4	1,269	-9.8	23	+1.8	Normal
S. K.	F	29	156	51.0	83	98.6	1,296	1,140	-12.0	1,160	-10.5	20	+1.8	Endocarditis
D. R.	F	34	162	111.8	68	97.6	1,865	1,592	-14.6	1,644	-11.8	52	+3.3	Obesity; cholecystitis
Average.....								+20.6	+20.7	+ 1.75	+0.53	

between the two series than the normal subjects. However, the difference was so slight that it was less than the difference between two tests made on the same patient on different days under identical conditions. Thus, N. W., on whom two experiments in the second series were conducted several days apart, gave the percentage difference of the two tests (one taken before and one after the meal) of -1.6 and $+8.3$, whereas the corresponding value for the experiment in the control series was $+2.7$. The difference in the production of heat brought about by the special breakfast on all the other patients was within the range of those already discussed. Thus our results are in agreement with those of Benedict¹ on normal subjects.

Based on the foregoing data, it is concluded that the special breakfast recommended by Benedict⁴ may be used with advantage to a patient who has a late appointment for a basal metabolic test. Such a breakfast may have the following advantages: (1) it may minimize the nervousness of the patient, which is usually caused by the prolonged waiting; (2) it may relieve the discomfort caused by hunger; and (3) it will enable laboratories to perform metabolic tests in the afternoon.

SUMMARY

Two series of experiments were conducted on three normal persons and on twenty-three subjects with a pathologic condition, including twelve patients with thyrotoxicosis. The basal metabolism varied from $+74.6$ to -14.6 per cent from the Harris-Benedict standard. In the control series two tests were made one hour apart, while in the second a special breakfast recommended by Benedict was given after the first test, followed by another test an hour later. The average difference of the two tests in the control series was 0.08 per cent while that of the second series was 0.53.

On the basis of our experimental data, we conclude that the special breakfast may be used with advantage to patients who are extremely nervous and who have late appointments for their basal metabolic test.

THE INTERMEDIATE METABOLISM OF FOREIGN SUGARS *

ELLA H. FISHBERG, M.D.

AND

B. T. DOLIN, M.A.

NEW YORK

The recent development of a rapid method for the estimation of foreign sugars in the blood in the presence of dextrose¹ throws new light on the chemical nature of the reducing substances circulating in the blood stream under normal and pathologic conditions. The methods that have previously been used for this determination fall into three classes: (1) physical methods (polariscopy, etc.), (2) chemical methods, dependent on the rate of reaction of the various sugars under fixed conditions, and (3) biologic methods which depend on the selective action of living organisms. The chemical reactions have not been sufficiently specific. It has been very difficult to get the sugar solution pure enough for physical measurements because of the variety and great number of other optically active substances always present in the blood.

The application of yeast fermentation, which theoretically should remove all the dextrose, has resulted in entirely conflicting data. Neuberg² attributed these discordant results to reducing and optically active substances formed during the fermentation, even when pure dextrose solutions and pure yeast cultures are used. Folin and Svedberg³ showed that eight minutes' incubation with yeast completely destroyed the blood dextrose. Somogyi found the reaction almost instantaneous, and that at room temperature a simple substitution of a 10 per cent (moist weight) yeast suspension, for the distilled water for laking and dilution in the Folin-Wu tungstic acid precipitation of the blood proteins, results in the total destruction of the dextrose in the blood, leaving intact other sugars such as xylose, galactose and lactose. This gives a method of estimating the actual content of the nonfermentable sugars in the presence of dextrose, where previously one could estimate only the total sugar. Certain problems in the intermediate metabolism of the foreign sugars become simplified; as, for instance, the extent to which the

* Submitted for publication, Jan. 7, 1930.

* From the Chemical Laboratory of Beth Israel Hospital.

1. Somogyi, M.: *J. Biol. Chem.* **75**:33, 1927.

2. Neuberg, C.: *Biochem. Ztschr.* **24**:430, 1910.

3. Folin, F., and Svedberg, A.: *J. Biol. Chem.* **70**:405, 1926.

foreign sugar tends to take the place of the normal dextrose and the amount of sugar actually liberated by the glycogenic depots in response to the stimulus of the dextrose hypoglycemia engendered by the foreign substance.

The rate of change of concentration (C) in the blood is dependent on four factors: the addition (α), the destruction (δ), the storage (ψ) and the excretion (ϵ).

$$\frac{dC}{dt} = \phi (\alpha, \delta, \psi, \epsilon)$$

α can be known and ϵ can be measured, but lack of knowledge of the interrelationships of δ and ψ makes it impossible to solve the differential equation. It is undoubtedly true that some of the nonassimilable sugar is excreted into the intestine and the bacterial destruction takes place there. In a sugar such as xylose or any of the other pentoses the main channel of excretion is through the kidneys, and a very high portion of it can be accounted for in this fashion. Hence any changes in the permeability of the kidney membrane should be of enormous importance in regulating the amount of pentose in the blood. The results of animal experimentation and also one case of nephritis show this to be true.

The changes in the concentration of galactose in the blood are influenced by more factors, since galactose is more closely akin to dextrose. Here the factor ψ comes into play to a larger extent. Galactose has been reported as able to relieve insulin intoxication⁴ and has a somewhat therapeutic effect in relieving the hypoglycemia following the total extirpation of the liver, as reported by Mann and Magath.⁵ Hence it is definitely changed in the liver into glycogen, which is able to respond to the stimulus of hypoglycemia to be converted into dextrose. The liver function tests with ingested galactose are based on the assumption that the healthy liver will dispose of a certain amount of foreign sugar in a definite time. However, it must always be kept in mind that the liver has amazing compensatory functional powers, and the presence of a minimum amount of normal tissue will still maintain normal function when the pathologic anatomic picture gives an appearance of almost total tissue destruction. Hence negative results are by no means conclusive of the absence of liver destruction. We have, however, found that in experimental phosphorus poisoning (when carried out over a period of from six to eight weeks and more) resulting in pathologic lesions similar to those found in man as a result of chronic liver disease, we could get much delayed destruction of the

4. Noble, E. C., and McLeod, J. J.: *Am. J. Physiol.* **64**:547, 1923.

5. Mann, F., and Magath, T.: *Studies on Physiology of Liver: Effect of Administration of Glucose in the Condition Following Total Extirpation of Liver*, *Arch. Int. Med.* **30**:171 (Aug.) 1922.

galactose administered. The kidney also disposes of some of the excess galactose, and in cases of chronic nephritis in man we could also get delayed disappearance of the galactose from the blood, as well as in experimental uranium nephritis in rabbits.

METHOD OF SUGAR DETERMINATION

A weighed amount of Fleischman's yeast was suspended in ten parts of water and repeatedly centrifugated till the supernatant liquid was clear and the last washing caused no reduction of copper solutions. The yeast was suspended in ten parts of water and kept in the icebox, being centrifugated every morning and the supernatant fluid being replaced by clear water.

TABLE 1.—*Distribution of Fermentable and Nonfermentable Reducing Substances in Normal Patients*

Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Dextrose, Mg. per 100 Cc.
103	21	79
74	31	43
113	32	81
73	31	39
81	22	62
88	29	59
74	31	43
89	26	63
112	21	88
107	25	82
92	27	65
111	29	82
121	29	95
101	21	77
86	28	58

Two cubic centimeters of blood was dropped into 2.3 cc. of water and 1 cc. of 33 per cent solution added and shaken for a minute. Then 0.5 cc. of tungstic acid (made by 0.5 cc. of two-thirds normal sulphuric and 0.5 cc. of 10 per cent sodium tungstate solution) was added and centrifugated. Of the clear fluid 2 cc. was used and the reducing substance determined by the Hagedorn-Jensen⁶ method. It is, of course, understood that the usual Folin method may be used, and in this case one part of blood with seven parts of 10 per cent yeast suspension, and then one part each of the sulphuric acid and sodium tungstate were added, and the filtrate used exactly as the usual Folin-Wu filtrate.

A series of determinations was done on cases selected at random from the wards, but not showing any disturbance in metabolism, as for example corneal ulcer, appendicitis, Colle's fracture, etc.

The average nonfermentable fraction for normal reducing substance of the blood is about 28 mg. per hundred cubic centimeters, which is

6. Hagedorn, H. C., and Jensen, B. N.: *Biochem. Ztschr.* **135**:46, 1923.

in agreement with the observations of Somogyi. In a second series of cases in which all patients were suffering from disturbances of metabolism, the ratio between the fermentable and the nonfermentable reducing substance of the blood was determined.

In table 2 it is shown, in agreement with the results of Somogyi, that in uremic patients with a high nonprotein nitrogen content of the blood, there is a distinct rise in the nonfermentable reducing substances. However, in the case of diabetic patients we found, in contrast with the figures given by Somogyi, a distinct rise in the nonfermentable

TABLE 2.—*Distribution of Fermentable and Nonfermentable Reducing Substances in Metabolic Disorders*

Disease	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Dextrose, Mg. per 100 Cc.	N. P. N.
Diabetes mellitus.....	212	84	128	...
Diabetes mellitus.....	208	38	170	...
Diabetes mellitus.....	194	45	149	...
Diabetes mellitus.....	495	90	405	...
Diabetes mellitus.....	201	49	152	...
Diabetes treated with insulin.....	109	40	169	...
Diabetes treated with insulin.....	121	34	87	...
Hypoglycemia (overdosage of insulin)...	41	24	17	...
Hypoglycemia (overdosage of insulin)...	34	23	11	...
Hypertension.....	184	41	143	...
Hypertension.....	176	39	137	...
Hypertension.....	164	38	126	...
Uremia.....	154	64	90	161
Uremia.....	182	51	131	131
Uremia.....	151	60	91	394

fraction, and we have found figures as high as 90 mg. per hundred cubic centimeters, in agreement with the results of Lund and Wolf.⁷ In cases of hypertension showing rather high figures of the total blood sugar, we found distinctly higher residual reducing values. In two cases of hypoglycemic shock, we found normal values of the nonfermentable reducing substance in agreement with the results found by van Slyke⁸ in the experimental hypoglycemia of rabbits.

Another series of cases that yielded high nonfermentable reducing substances in the blood was that of women in the late stages of pregnancy. These figures were especially high, reaching between 70 and 90 mg. per hundred cubic centimeters just before and during labor.

7. Lund, G. S., and Wolf, C.: *Biochem. J.* **20**:263, 1926.

8. Hiller, A.; Linder, G. C., and Van Slyke, D. D. *J. Biol. Chem.* **64**:625, 1925.

FATE OF FOREIGN SUGARS INJECTED INTO THE BLOOD
STREAM OF RABBITS

Varying amounts of sugar were injected into the marginal veins of rabbits and the blood taken at intervals by simple incision of the vein in the opposite ear.

It has been found by one of us⁹ that the rate of disappearance of the sugar is proportional to the concentration of the sugar itself which is decreasing.

$$\frac{dc}{dt} = -K C$$

Separating the variables and integrating, we have

$$C = Ae^{-Kt}$$

where K is a constant dependent on the unit of time used, and A should be roughly dependent on the amount injected into the blood and the particular method used for the estimation of the sugar. Using any two values of C , we can eliminate A and get a numerical value for K which was found to be 1×10^{-1} . Using this value, we can solve for A . It can be seen from tables 3 and 4 that the value of A is constant with the limits of biologic accuracy. The constancy of A is alike proof of the constancy of K and the correctness of the form of the equation used.

It is at once apparent that the equation $C = Ae^{-Kt}$ is that governing the velocity of a monomolecular chemical reaction. It is thus possible to determine the concentration of the nonfermentable reducing substance at any time in the blood when its concentration at any definite time is known, since the logarithm of the concentration of the foreign sugar at any time is proportional to the time after injection.

Ten milligrams of uranium acetate was injected into a rabbit, and the morning after, the same rabbit was given 2.5 Gm. of xylose injected into the marginal vein. The excretion of the nonfermentable sugar was much delayed through the damage to the kidney tubules. At the end of five hours, the nonfermentable fraction of the blood-reducing substance was still 101 mg. per hundred cubic centimeters. Another rabbit was given subcutaneously into the skin of the abdomen 1 Gm. of phlorizin in two divided doses. On the following day, the animal was excreting 3.4 per cent of sugar in the urine; 2.5 Gm. of xylose was then injected into the ear of this rabbit, and blood taken at intervals and examined for sugar. The nonfermentable reducing substance disappeared from the blood at a much quicker rate than normally, owing to the increased permeability of the kidney membrane caused by the phlorizin (tables 3, 4 and 5 and chart 1). The results are essentially

9. Fishberg, E. H.: J. Biol. Chem. 86:665, 1930.

TABLE 3.—*Results of Injection of Xylose into the Marginal Vein of Rabbits*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	e-kt	A
Before	114	30	84
10	308	233	75	0.905	258
50	267	143	124	0.607	234
85	222	100	122	0.427	234
115	216	79	137	0.317	249
165	174	48	126	0.192	250
220	134	22	112
Injection of 2.5 Gm. of Xylose into Rabbits with Nephritis Caused Uranium					
Before	124	31	93
10	315	241	74
30	268	175	93
60	254	160	84
180	221	150	61
300	200	159	41
480	174	101	73
Injection of 2.5 Gm. of Xylose into a Rabbit with Phlorizin Diabetes					
Before	129	27	102
20	439	304	135
45	373	194	179
70	211	83	123
110	185	57	128
140	169	24	145
170	112	34	78

TABLE 4.—*Results of Injection of 5 Gm. of Galactose into a Rabbit*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	e-kt	A
Before	121	32	89
5	440	323	117	0.951	339
30	343	230	113	0.741	312
60	331	170	164	0.549	310
90	251	124	127	0.407	307
120	190	96	94	0.301	314
180	181	52	129	0.165	317
225	162	34	128	0.105	338

TABLE 5.—*Results of Injection of 3 Gm. of Galactose into a Rabbit*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	e-kt	A
Before	120	28.5	91.5
12	320	248.0	72.0	0.980	253
15	320	189.0	131.0	0.861	223
35	242	160.0	82.0	0.705	228
65	210	112.0	98.0	0.522	218
95	191	86.5	115.5	0.387	222
140	191	54.5	136.5	0.247	221

similar to those obtained by Corley.¹⁰ We also tried the effect of a dose of chloroform (1 cc. administered the evening before), but could find no indication of a changed rate of excretion of nonfermentable reducing substance in the blood. A negative result in this case cannot be interpreted as proof that the intermediate metabolism of xylose is independent of the liver function, because it is well known that even in cases of extreme anatomic damage to the liver, the liver possesses such great compensatory powers that the loss of function is not noticeable.

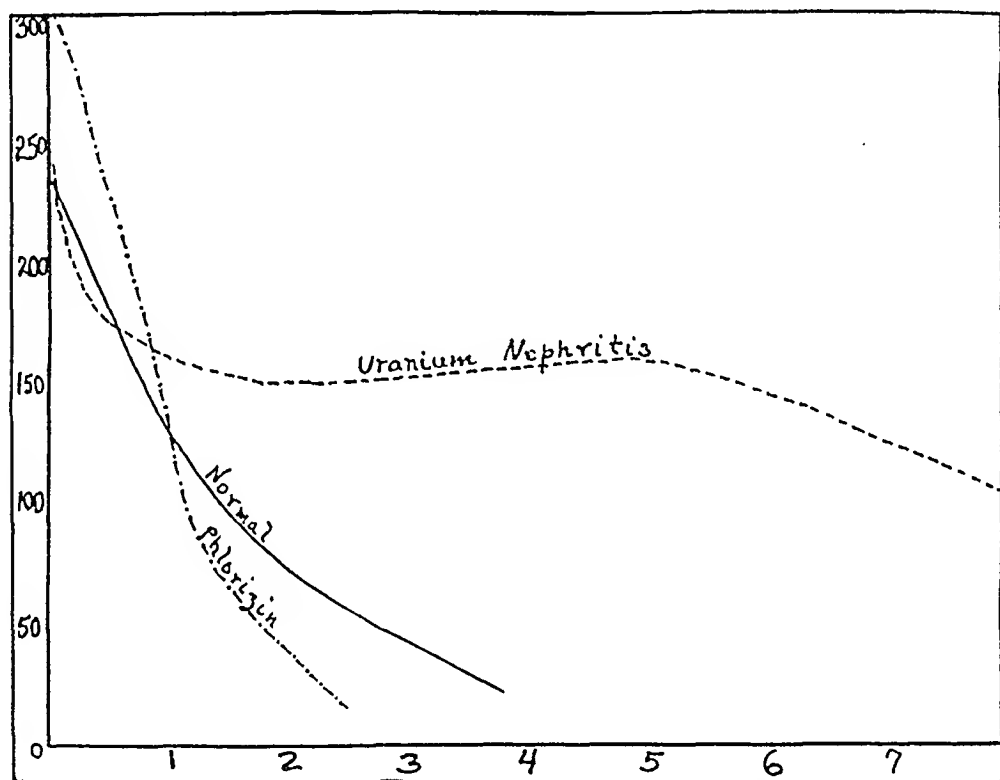


Chart 1.—The effect of an injection of 3 Gm. of xylose into the marginal vein of a rabbit.

A patient having acute nephritis was given 30 Gm. of xylose by mouth. After four hours the reducing, nonfermented fraction of the blood was still above normal. From what is at present known of its intermediate metabolism, xylose should be ideal for a kidney permeability test. However, its present cost makes this difficult.

Three grams of galactose was injected into rabbits and the fermentable and nonfermentable reducing substance measured at intervals thereafter. Five grams of galactose was then injected into another rabbit. It can be seen from tables 4 and 5 that *A* remains constant and is proportional to the amount injected. Rabbits that had been

10. Corley, R. C.: J. Biol. Chem. **70**:521, 1926.

treated with 10 mg. of uranium acetate were given injections of the same amount of galactose. We noticed a slight delay in the excretion of the galactose as the reducible nonfermenting fraction of the sugar remained for over five hours at a high level. Corley¹¹ attempted to see if there was any delay in the process of excreting the nonfermentable fraction after one dose of phosphorus. He found that this had no effect, and we were able to confirm his results. However, in those rabbits which had been given phosphorus for six weeks previously, two drops a day, we found a distinct delay in the utilization of the

TABLE 6.—*Results of Injection of 3 Gm. of Galactose into a Rabbit Suffering from Phosphorus Poisoning*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.
Before	118	27	91
2	308	294	114
30	274	231	43
60	231	173	58
90	210	123	87
120	181	114	70
180	201	110	91
360	215	101	114

TABLE 7.—*Results in a Human Being of 60 Gm. of Galactose by Mouth*

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.
Before	80	28	52
45	154	133	21
90	250	148	102
135	125	63	62

galactose, the blood showing, after six hours, a residual reduction of 115 mg. per hundred cubic centimeters (table 6).

Sixty grams of galactose ingested by a normal man results in a rise of the total blood sugar to about 250 mg. per hundred cubic centimeters within one and a half hours, and then a sharp fall, so that in two and a half hours, the blood again contains only its normal sugar content (table 7; chart 2). The nonfermentable fraction of the blood rises to a maximum more quickly, reaching there in approximately three quarters of an hour, and stays at that point, giving the typical plateau curve, to one and a half hours, and falling also to reach its

11. Corley, R. C.: J. Biol. Chem. 74:1, 1927.

normal value within two and a half hours. The fermentable fraction of the blood falls from its normal value at first, probably owing to the flooding of the blood with galactose causing a smaller mobilization of dextrose from the liver. The fermentable fraction reaches its minimum at the time the nonfermentable fraction reaches its maximum. There then comes a sharp rise in the fermentable fraction due to the stimulus of the dextrose hypoglycemia, which reaches its maximum in about one and three quarter hours, and then falls to reach its normal value within two and a half hours.

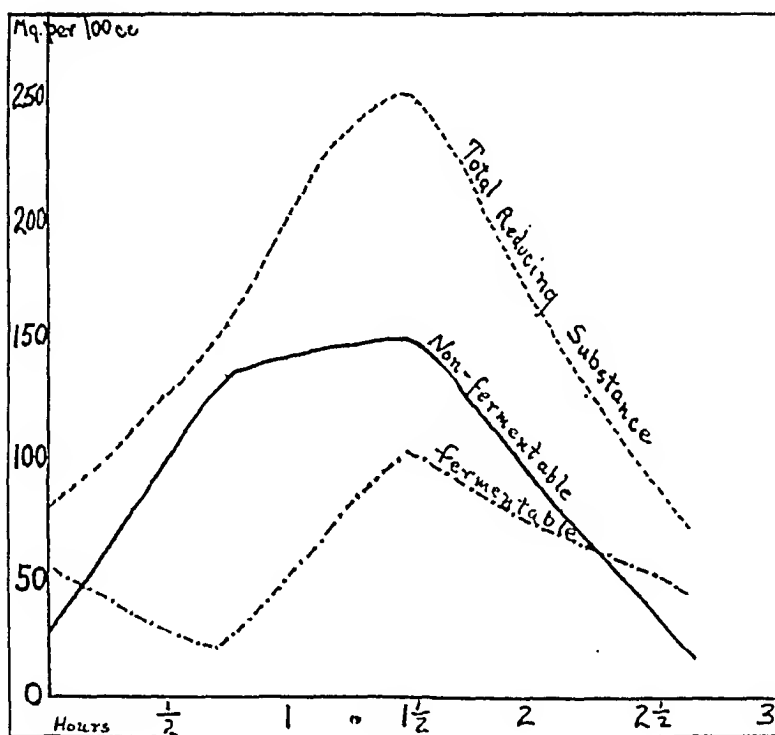


Chart 2.—The effect of the galactose tolerance test in a normal man.

On the ingestion of 60 Gm. of galactose by a patient with diabetes (table 8; chart 3), the total blood sugar rises to a much higher level than that in a normal person, reaching 450 mg. per hundred cubic centimeters. It also reaches this level more slowly. It falls more slowly to its value before the ingestion of the galactose, only reaching the approximate value after four hours. The nonfermentable reducing substance reaches its maximum at the same time as the normal, but tends to stay there, not falling within four hours. In our experiments, the reducing fermentable fraction fell at first and then rose to reach a very sharp maximum in two hours, which, however, was more than

TABLE 8.—Results in a Diabetic Man of 60 Gm. of Galactose by Mouth

Time, Minutes	Total Reducing Substance, Mg. per 100 Cc.	Fermentable Reducing Substance, Mg. per 100 Cc.	Nonfermentable Reducing Substance, Mg. per 100 Cc.
Before	183	112	71
30	192	105	87
90	259	76	183
120	400	230	170
180	242	75	167

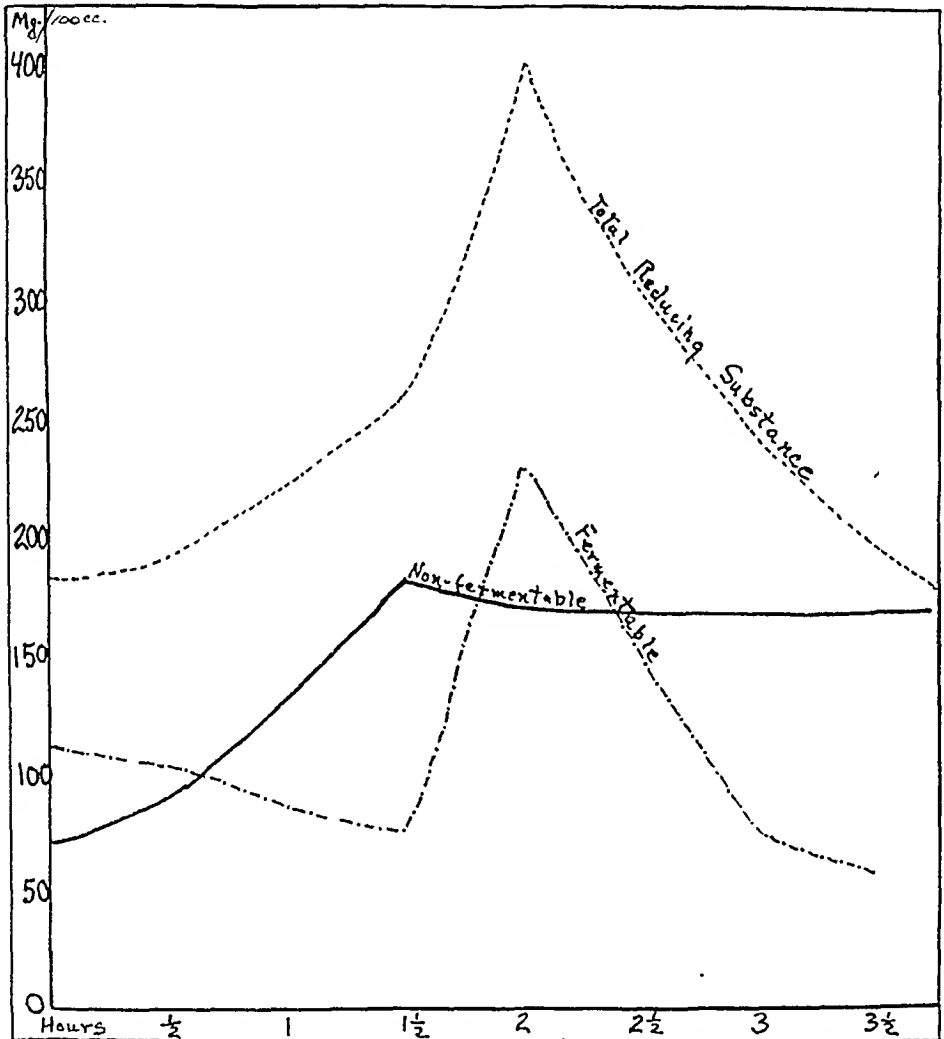


Chart 3.—The effect of an injection of 60 Gm. of galactose into a patient with diabetes.

twice as high as that reached in the normal person. It took three hours for the fermentable sugar to reach its previous value.

Hamman and Hirschmann¹² expressed the view that certain forms of nephritis may affect carbohydrate metabolism. Sixty grams of

12. Hamman, L., and Hirschmann, I. : Blood Sugar, Arch. Int. Med. 20:761 (Nov.) 1917.

galactose was given by mouth to a patient with nephritis and hypertension, and a delay in the utilization or excretion was found because it took four hours for the reducing nonfermentable substance of the blood to come down to its level of 85 mg. per hundred cubic centimeters. Whether this retention is to be ascribed primarily to the nonpermeability of the kidney membrane or the changed condition of the blood vessels cannot be decided (chart 4).

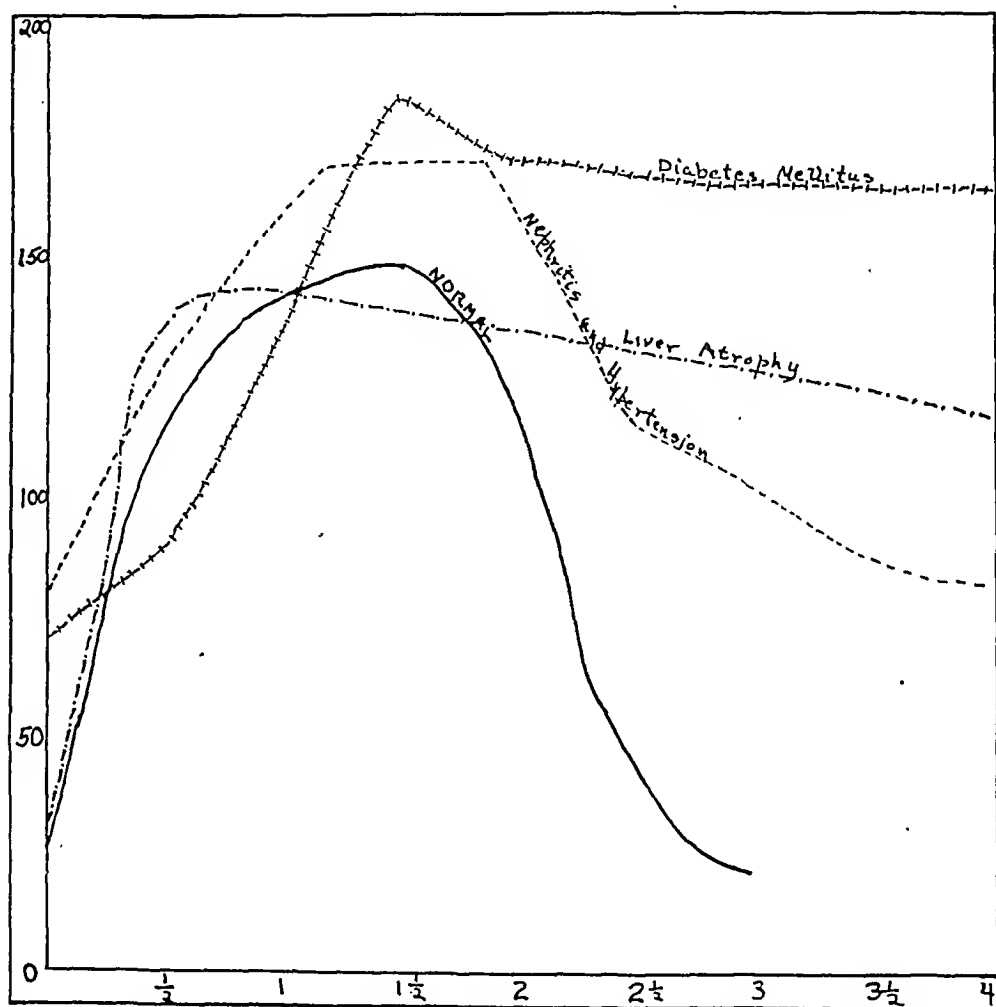


Chart 4.—The ingestion of 60 Gm. of galactose (nonfermentable reducing substance).

SUMMARY

A method is given for the separate determination of xylose and galactose in the presence of dextrose in 0.2 cc. of blood.

The reducing nonfermentable fraction of the blood is remarkably constant in normal human beings, amounting to about 28 ± 5 mg. per hundred cubic centimeters, while in uremia, diabetes, nephritis and lactation this is increased.

Galactose and xylose introduced directly into the blood stream of rabbits disappears at a rate proportional to the actual concentration of the sugar in the blood in accordance with the law governing the velocity of a monomolecular equation. It is thus possible to calculate the non-fermentable reducing substance in the blood at any time, since the logarithm of the concentration of the sugar at any moment is proportional to the time after injection.

Xylose disappears much more slowly from the blood stream of rabbits suffering from uranium nephritis and more quickly from rabbits made diabetic by phlorizin.

Galactose disappears more slowly from the blood stream of rabbits suffering from uranium nephritis and from the blood of those gradually poisoned by phosphorus.

In human beings, galactose disappears more slowly from the blood of patients with nephritis and diabetes.

EPIGASTRIC PULSATION

CLASSIFICATION IN REGARD TO THE FORM OF THE EPIGASTRIOGRAM *

NOBUTATSU FUKUI, M.D.

TOKIO, JAPAN

In a former report, I gave only an outline¹ of my investigation on the epigastric pulsation and its clinical application in the diagnosis of arrhythmia cordis.² Later I explained in detail³ some new problems of epigastric pulsation, in which the epigastric pulsation was investigated as a physical phenomenon from a statistical point of view as well as in relation to the orthodiagram of the heart. In this paper, I shall give the results of the latter report³ first and then a new classification of the forms of epigastriograms.

STATISTICAL AND ORTHODIAGRAPHIC STUDIES

For the statistical research, the epigastric pulsation is classified into five types, *A*, *B*, *C*, *D* and *E*, as shown in the accompanying table.

Classification of Epigastric Pulsation

			In Ordinary Respiration	In Deep Inspiration
Persons with pulsation (P.)	With marked pulsation = marked P.	A	Marked	Marked
	With moderate pulsation = moderate P.	B	Moderate	Marked
	With slight pulsation = slight P.	C	Slight	Moderate
Persons with nonpulsation (N. P.)	With relative nonpulsation = relative N. P.	D	Missing	Slight
	With absolute nonpulsation = absolute (N. P.)	E	Missing	Missing

Examination of 2,000 healthy men, from 12 to 60 years old, showed that all types of pulsation in those under 20 years of age remain almost constant. Relative nonpulsation (*D*) occurred in 60 per cent; slight pulsation (*C*) in from 20 to 30 per cent; moderate pulsation (*B*) and

* Submitted for publication, Dec. 11, 1929.

* From the Kaigun Medical College, Tsukiji, Tokyo.

1. Fukui, N.: On the Epigastric Pulsation, *Acta scholae med. univ. imp. Kioto* 7:41, 1924.

2. Fukui, N.: Epigastric Pulsation; the Diagnosis of the Arrhythmia Cordis Through the Epigastriogram, *Arch. Int. Med.* 38:360 (Sept.) 1926.

3. Fukui, N.: Ueber die epigastrische Pulsation, *Wien. Arch. f. inn. Med.* 15:349, 1929.

absolute nonpulsation (*E*) in approximately from 5 to 10 per cent; marked pulsation (*A*) was almost missing at this age. In persons over the age of 40 the moderate pulsation (*B*) was present in more than 30 per cent and relative nonpulsation (*D*) in less than 20 per cent. The number of persons with manifest pulsation (*A*) showed a sudden increase. This change begins at the age of 25 to 30 years, and the age of transition from nonpulsation to pulsation should be about 30. Absolute nonpulsation (*E*) was less than 10 per cent in all persons of all ages examined.

The relation between the epigastric pulsation and the proportion between height and chest contour was investigated from the statistical point of view, and it was found that in persons throughout the whole range of ages examined the proportion is always bigger in persons with nonpulsation (N.P.) than in those with pulsation (P).

For details of the investigation of the relation between epigastric pulsation and the orthodiagram of the heart some technical terms have been applied. For instance, the figure indicating the relation between the heart and the subcostal angle is called scrobocardiac figure; the area of the heart included in the subcostal angle is called the grave area; the percentage of the grave area to the entire area of the heart is called area percentage, the distance between the apex of the subcostal angle and the middle of a line formed by the lower border of the heart and subcostal angle is called ptosis distance.

These factors can be measured in two ways, not only in regard to the pulsation (persons with pulsation [P.] and those with nonpulsation [N.P.]), but also in regard to the age (persons over 30 years and those under this age). In these four groups, orthodiagraphic measurement of the heart was made, i. e., breadth, length, inclination, heart area, grave area, area percentage, breadth of radix aortae and ptosis distance and many other factors were measured. The intensity of the epigastric pulsation is related more closely to the area percentage than to the grave area. It is also very interesting to note that the breadth of the aortic root is approximately the same as the ptosis distance, and the epigastric pulsation is related to these two factors; i. e., if the breadth of the aorta is longer than the ptosis distance, the pulsation is weak or missing, and if the latter is longer than the former, the pulsation is stronger.

In the examination of 2,000 healthy men, I found some with asymmetry of the processus xyphoideus. The process deviates to the right side, so that the space between the left costal bow and the process becomes enlarged. In these cases, the ptosis distance is long, the grave area is large, and the epigastric pulsation is intensive (fig. 1).

The registration of the epigastric pulsation is very easy. Just like the venous pulse, it is registered by applying the funnel over the

pulsating area or recorded by Frans' light reflex. The epigastric pulsation is related to respiration, being strong at inspiration and feeble at expiration, this action being opposite to that of the apex beat. By applying this effect of the respiration, the intensity of the pulsation is sometimes controlled in recording it when it is too strong or too weak. In addition to the respiration, the position of the body and the contour of the epigastric region interfere with the epigastriogram.

Analysis of the epigastriogram shows the following components: first, the *a* wave rises, appearing simultaneously with the auricular

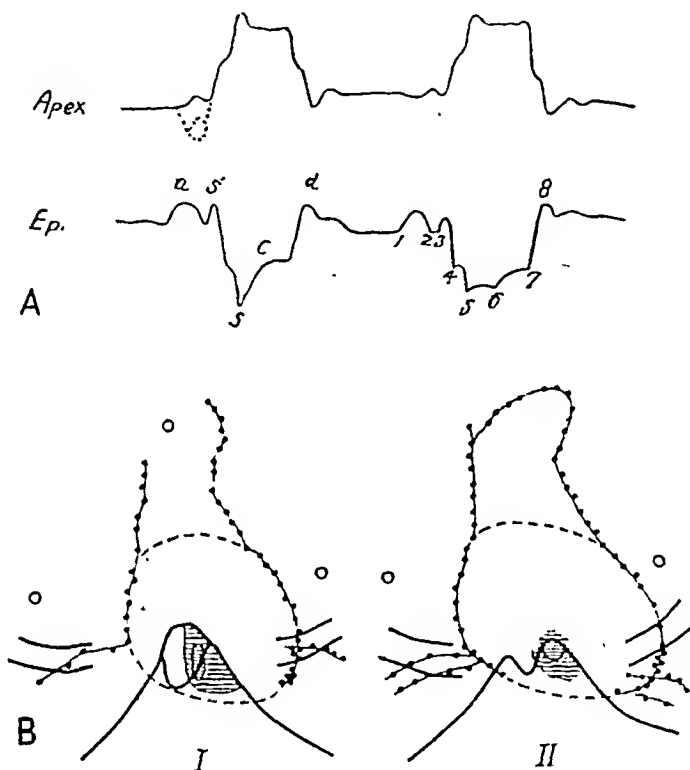


Fig. 1.—In *A*, a typical form of the epigastriogram (Fukui) is compared with that of the apex beat (Wenckbach). The form consists of many components as follows: 1-2, auricular systole (*a* wave); 2-3, intersystole; 3-4, intersystole; 4, opening of the semilunar valves; 5, pulsation of the abdominal aorta (*c* wave); 6, *c* wave, which appears seldom in dissociated wave; 7, the end of the systole; 7-8, the beginning of the diastole (*d* wave). *B* shows scrobocardiograms, in which the processus xyphoideus deviates to the right, and the center of the pulsation lies in the wide space between the left costal bow and the process.

contraction; second, the *s* wave, owing to the muscular shock at the beginning of the ventricular systole, rises sharply and then falls to the *s* valley; third, the *c* wave appears, owing to the pulsation of the abdominal aorta.

The epigastriogram, which consists of the *a*, *s*, *d* and *c* waves, can also be applied to the diagnosis of arhythmia cordis in the same manner as the jugular venous pulse. This is not only very convenient, espe-

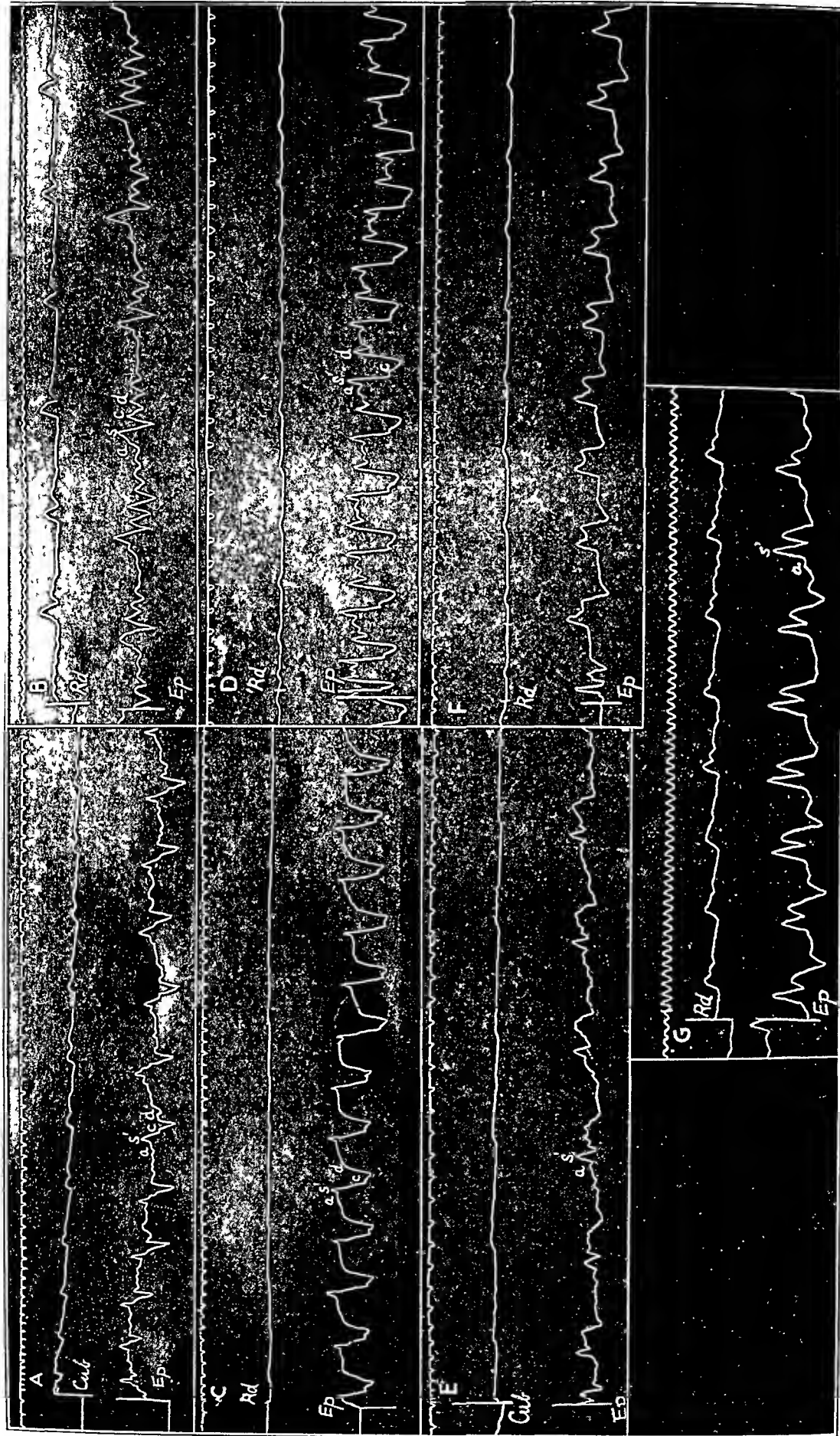


Fig. 2.—Epigastriograms with high *s* waves. In *A* and *B*, epigastriograms recorded at inspiration of healthy men, the *s* wave is relatively high but cannot yet be called the partially positive form. *C* and *D* are epigastriograms of young men of asthenic constitution. This form, in which the plateau from the *d* wave to the *s* wave rises high, is often registered by the asthenic person. *E*, registered at the deep inspiration of athletic young men, is called the partially positive form, in which the *s* wave is highest. *F* and *G*, registered in a case of mitral failure with intensive hypertrophy and dilatation of the left and of the right sides of the heart, show here almost the same figure with the apex beat, for the *s* wave changes into a wide plateau during the ventricular systol and the *d* wave falls into the base line instead of the diastolic plateau.

cially in cases in which the jugular venous pulse is difficult to register, but also very advantageous on account of the *s* wave, which is missing in the venous pulse.

FORMS OF THE EPIGASTRIOGRAMS

In the former report epigastriograms were classified into various types; for instance, those typical for the asthenic constitution, for pulmonary emphysema, for beriberi, for aortic insufficiency, etc. It must be confessed that this kind of classification is not entirely accurate, and the application of these types of epigastriograms in the diagnosis of the diseases themselves is still less practicable.



Fig. 3.—Epigastriograms with high *d* waves. In *A*, registered in old men and *B* in old men with bronchial asthma, the *d* wave is highest and the *a* wave also shows manifest elevation.

In this paper the epigastriograms will be classified chiefly in regard to the characteristic of each wave itself, and the epigastriograms will be divided into different types, for instance, an epigastriogram with a high *a* wave, a high *d* wave, a high *s* wave or a high *c* wave. These will be discussed, and some figures will be presented for each group, with explanations.

Epigastriogram With a High S Wave.—The *s* wave is caused by the muscle shock at the beginning of the ventricular systole, and the later greater part of the systole forms the wide *s* valley, in which the pulsation of the abdominal aorta appears. The direction of the movement of the left side of the heart in the ventricular systole is just the opposite of that of the right side of the heart; i. e., the *s* wave is formed by the movement of the left side of the heart and by the abrupt muscle shock

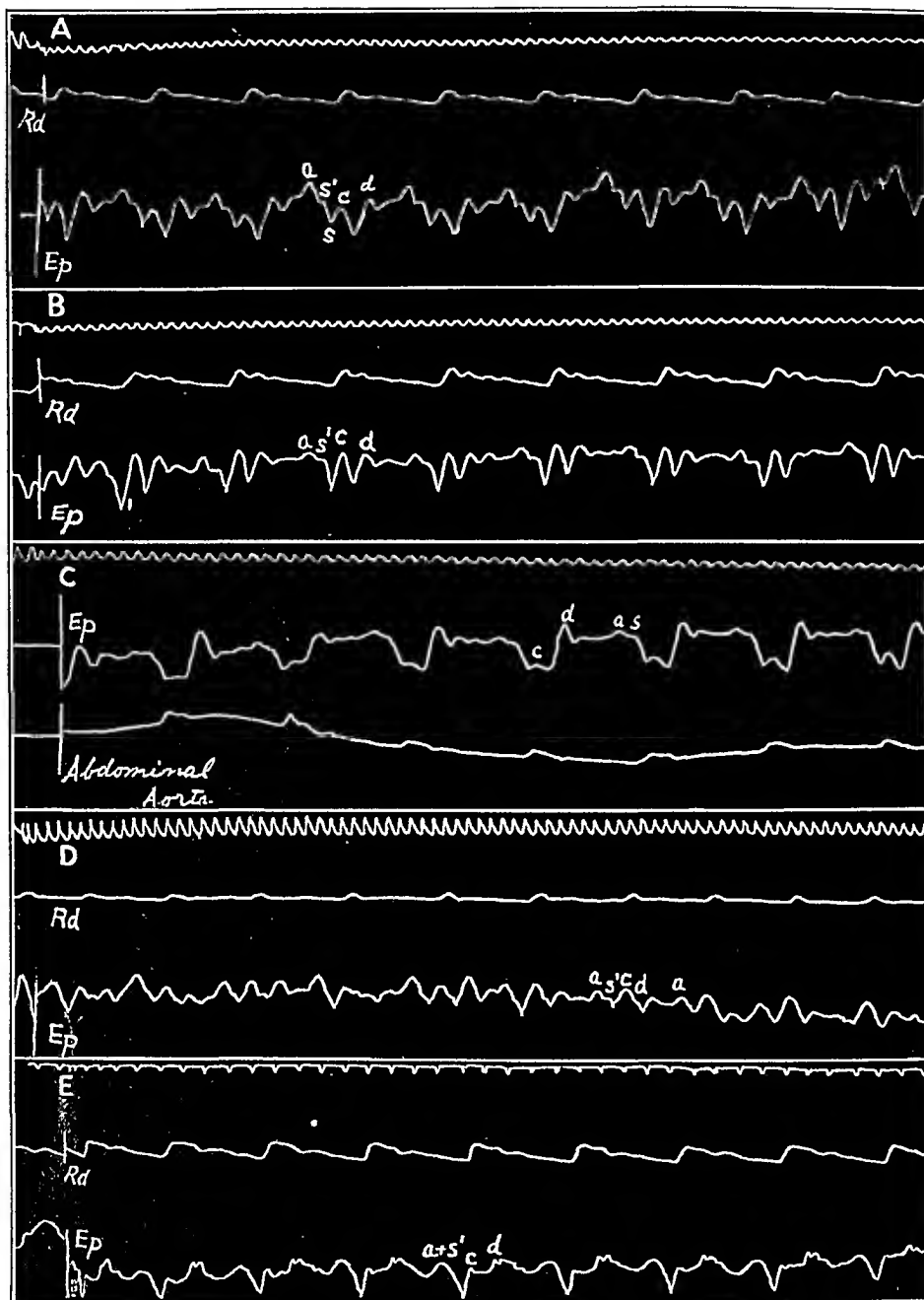


Fig. 4.—Epigastrigrams with high *a* waves. *A* and *B* were registered in asthenic young men and *C* in old men with pulmonary emphysema. All these persons have no definite diseases and yet have such a manifest epigastric pulsation, in which the *a* wave rises sharply. *D* and *E*, recorded in cases of beriberi, show a very high *a* wave, which is characteristic for that condition, in addition to other waves, which also rise sharply. The marked elevation of the *a* waves in beriberi is due to the hypertrophy and dilatation of the right side of the heart, which occupies the grave area.

in the beginning of the ventricular systole, while the *s* valley mainly represents the direction of the movement of the right side of the heart.

The sharp rise of the *s* wave means that the movement of the left side of the heart is brought to the epigastrium more easily. The *s* wave rises sharply in the inspiratory phase of the breathing of the normal person, because at inspiration the heart takes the position of the drop heart and the apex of the heart approaches the pulsating heart

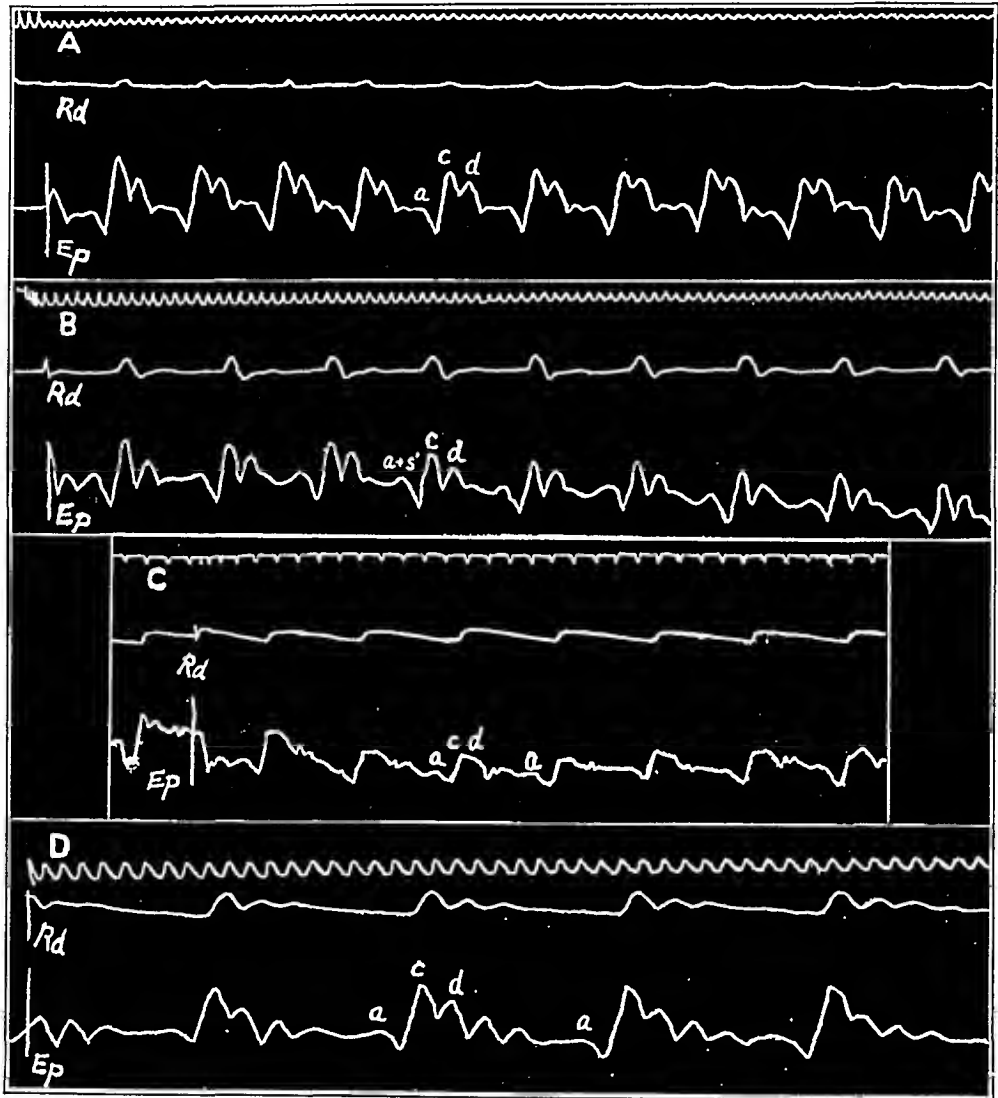


Fig. 5.—Epigastragrams with high *c* waves. *A* and *B*, recorded in patients with fever and *C* and *D* in cases of aortic insufficiency, show high peaks of the *c* wave; *C* and *D* especially are characteristic of aortic insufficiency and have a diagnostic value.

grave. Thus the movement of the apex part and of the anterior left side of the heart, which both represent the movement of the left side of the heart, is led more easily to the scrobiculum cordis. The abrupt change in the direction of the movement of the left side of the heart,

due to the muscle shock, appears in the epigastrigram as a high *s* wave. The inspiratory rise of the *s* wave is apt to occur in the epigastrigram of healthy young persons with hypertrophy of the left side of the heart, especially in the athletic heart. This is due to the same factor as the positive epigastrigram, described later; for the epigastrigram with a high *s* wave is called the partially positive type. It is also interesting to note that a high *s* wave is sometimes obtained in cases of young asthenic persons with drop heart. The high *s* wave is due to the same condition as in the inspiratory phase of breathing. Naturally, this type of epigastrigram is obtained in many other heart diseases in which there is hypertrophy of the left ventricle.

The positive form is the casting figure of the normal epigastrigram, for in the ventricular systole the *s* wave goes into the positive wave instead of falling into the *s* valley, and the *d* wave forms a negative wave. The *c* wave is involved in the systolic swelling and is undetectable, while the *a* wave as a rule appears more distinctly than in the cardiogram for the apex beat. There are, of course, many transitional forms between the positive and the partially positive form; generally speaking, these are due to the same thing, but the positive form is more marked and therefore does not appear so frequently as the partially positive form. The positive form of the epigastrigram is seen in cases of heart disease with greatly hypertrophied and dilated left ventricles, while in normal healthy persons such an epigastrigram is rarely seen. It is interesting to note that the positive form is often seen in cases of decompensation due to mitral failure. But the positive venous pulse, which is characteristic for the arrhythmia perpetua, is due to a totally different cause than that of the positive epigastrigram.

Epigastrigram With a High D Wave.—The *d* wave is formed by the sudden change of the beating of the ventricle, especially of the right, due to the slackness of the heart muscle at the beginning of the ventricular diastole.

The marked rise of this wave has less meaning than that of the other waves. The rise is occasionally seen in the epigastrigram in cases of emphysema and therefore often in the epigastrigrams of aged persons. The probable reason for this is the large grave area due to the cardiopneumosis in emphysema.

Epigastrigram With a High A Wave.—Two factors are given as an explanation of the *a* wave: First, the contraction of the right auricle has an effect on the epigastrium, as shown in the appearance of the *a* wave, just as the contraction of the left auricle has an effect on the *a* wave as shown in the esophagocardiogram, because a small part of the right auricle often lies in the grave area or at least close to it. Second, a sudden change of the volume of the right ventricle due to the

sudden inflow of blood at the contraction of the right auricle is possibly another cause of the *a* wave.

The high peak of *a* wave of the epigastriogram occurs either in cases in which an increased contraction of the right auricle is called for (in many heart diseases, especially typical of the heart in beriberi), or in healthy persons who have a long ptosis distance and a large area percentage, without abnormalities either in the contraction of the right auricle or in the circulation of the lungs. The manifest rise of *a* wave is so typical in beriberi that it often aids in the diagnosis of this condition. This is very interesting in Japan, but the details will be omitted as they have been related in former reports.⁴

Epigastriogram With a High C Wave.—The pulsation of the abdominal aorta not only is an important component of the epigastriogram, but in certain diseases is the determining factor. The *c* wave appears in the *s* valley, a little later than the radial and a little earlier than the carotid pulse, or just between the two pulses. It always serves for the orientation of the epigastriogram. A sharp rise in this wave occurs first in the pulsus celeris, especially in cases of aortic insufficiency, in which the *c* wave is quite typical and has a diagnostic value.

Another noteworthy factor in the high *c* wave is the thin abdominal wall. The aortic pulsation is more easily transmitted, and thus in the case of exophthalmic goiter with emaciation or in an emaciated hyperemic patient, the epigastric pulsation consists almost entirely of the aortic pulsation, which is seen all over the abdominal wall.

Summary of Results.—The epigastriogram is here classified according to its form, for instance, the epigastriogram with a high *s* wave, with a high *d* wave, with a high *a* wave and with a high *c* wave.

The epigastriogram with a high *s* wave changes to the partially positive and the positive form. In healthy persons and especially in persons with athletic hearts the *s* wave rises sharply on inspiration. The positive form is found mainly in heart diseases accompanied by hypertrophy and dilatation of the left side of the heart. The epigastriogram with a high *d* wave has less meaning, often being obtained in the epigastric pulsation of pulmonary emphysema. The epigastriogram with a high *a* wave is recorded not only in cardiac diseases with dilatation of the right side of the heart, but also quite often for healthy persons with a large grave area and ptosis distance. The great rise of the *a* wave is characteristic in beriberi and often serves in the diagnosis of this condition. The epigastriogram with a high *c* wave is obtained in cases of marked celerity in the pulsation of the abdominal aorta, for instance, in patients with fever or with aortic insufficiency; in the latter condition it is typical and has often a diagnostic value.

4. Shimazono, J.: Beriberi, in Stepp and Görgy: Avitaminose und verwandte Krankheit Zustände, Berlin, Julius Springer, 1927, p. 539. Fukui (footnote 3).

GASTRIC SEQUELAE OF CORROSIVE POISONING *

WILLIAM S. BOIKAN, M.D.

AND

HARRY A. SINGER, M.D.

CHICAGO

The immediate effects of corrosive poisoning are well known by the general profession and are fully treated in books on toxicology. The remote results of corrosive ingestion with regard to the esophagus are likewise well understood and extensively dealt with in both periodicals and texts. Concerning gastric sequelae of corrosive poisoning, however, little has been written, especially in the English language. A careful search through the medical indexes for the past fifteen years published in this country or Great Britain yielded few references to late gastric lesions following corrosive poisoning. Halstead¹ told briefly of a midgastric stenosis with obliteration of the pyloric canal following the ingestion of sulphuric acid. Vinson and Hartman² discussed a case in which esophageal stenosis effectively treated by dilatation was followed within six months by pyloric stenosis which led to death. Vinson and Harrington³ reported a case of cicatricial obstruction of the stomach following poisoning with formaldehyde and referred to only one other case of corrosive constriction of the stomach, that of Vinson and Hartman.^{2,3}

From the paucity of reports in American and British medical journals one is led to infer that late structural changes in the stomach following corrosive poisoning are of rare occurrence. The facts, however, do not substantiate this inference. A not inconsiderable number of cases is reported from the continent in countries in which the incidence of corrosive ingestion is no higher than in ours. Furthermore, within less than a year and a half we have encountered at the Cook County Hospital five instances of late gastric stenosis following ingestion of

* Submitted for publication, Dec. 13, 1929.

* From the Departments of Pathology and Medicine, University of Illinois College of Medicine, and the Cook County Hospital Laboratories.

1. Halstead, A. E.: Pyloric Stenosis Following Sulphuric Acid Poisoning, *Surg. Clin. Chicago* **1**:495 (June) 1917.

2. Vinson, P. P., and Hartman, H. R.: Pyloric Obstruction Due to Swallowing Solution of Concentrated Lye, *M. Clin. North America* **8**:1037 (Jan.) 1925.

3. Vinson, P. P., and Harrington, S. W.: Cicatricial Stricture of the Stomach Without Involvement of the Esophagus Following the Ingestion of Formaldehyde, *J. A. M. A.* **93**:917 (Sept. 21) 1929.

acid or lye. That this experience is not unique is borne out by observations made elsewhere and recorded in connection with other phases of gastric disease. For instance, although mention of corrosive poisoning is not included in the index to Crohn's ⁴ book on diseases of the stomach, in the chapter on gastritis three cases of late corrosive lesions of the stomach are alluded to but are discussed from the standpoint of prognosis of gastritis.

Although gastric stenosis is not an infrequent sequel of corrosive poisoning, little information on the subject is available in our literature. One might conclude from this lack of information that gastric sequelae following corrosive poisoning possess no distinctive features and that each case is practically an entity in itself. That this conclusion is incorrect is indicated by the five cases to be reported, in each of which a characteristic syndrome can be readily identified.

REPORT OF CASES

CASE 1.—F. R., a white man, aged 41, entered the hospital, June 10, 1928, with the history of having been in good health until the day of entrance, when, shortly after his noon meal he swallowed nitric acid in mistake for liquor. Almost immediately, he experienced a burning sensation in the epigastrium, and within thirty minutes after ingestion he vomited an irritating fluid. On entrance to the hospital, he complained of persistent epigastric distress and vomiting after eating. Examination disclosed oral and pharyngeal corrosion and epigastric tenderness. Chemical analysis of the gastric washings showed the presence of nitric acid. The patient responded favorably to treatment and after four days refused to remain any longer in the hospital. He was warned of the possibilities of gastric stenosis and admonished to return at the beginning of symptoms of obstruction.

The patient was readmitted to the hospital on July 12, 1928. He stated that after leaving on June 14, he felt relatively well for about three weeks. During the week prior to his second entrance, he suffered from considerable epigastric pain and a burning sensation, vomiting of a projectile type and obstipation. On examination, epigastric prominence due to a distended stomach was readily outlined. There were no visible peristaltic waves. Moderate epigastric tenderness was elicited. A test aspiration performed on admission yielded 900 cc. of fluid with no free and 13 degrees of total acidity. On the following morning, after a night's fasting, 1,000 cc. of gastric contents was aspirated, this time showing 15 degrees free and 27 degrees total acidity. Roentgenographic examination (fig. 1) revealed a normal esophagus and a greatly dilated atonic stomach. Projecting from the lesser curvature was a nipple-like process which was interpreted as the pylorus drawn upward toward the cardia following cicatricial shortening of the lesser curvature. No barium was seen to leave the stomach during a protracted fluoroscopic observation.

Operation was advised and performed by Dr. Karl A. Meyer, who found that the pylorus was thickened, narrowed and distorted. A gastro-enterostomy was performed with difficulty, owing to the friability of the tissues. The patient

4. Crohn, B. B.: *Affections of the Stomach*, Philadelphia, W. B. Saunders Company, 1927, pp. 781-782.

developed pneumonia postoperatively and died. Permission for a postmortem examination was not granted.

CASE 2—I. P., a white man, 37 years of age, previously in good health, entered the hospital on June 6, 1928. He stated that four days prior to entrance, shortly after his evening meal, he swallowed some dilute sulphuric acid which he had mistaken for castor oil. He began to vomit within thirty minutes. A physician was called, who performed gastric lavage. When admitted, the patient complained of sore mouth and inability to swallow solids but no marked gastric distress. Examination revealed ulceration and sloughing of the lining of the

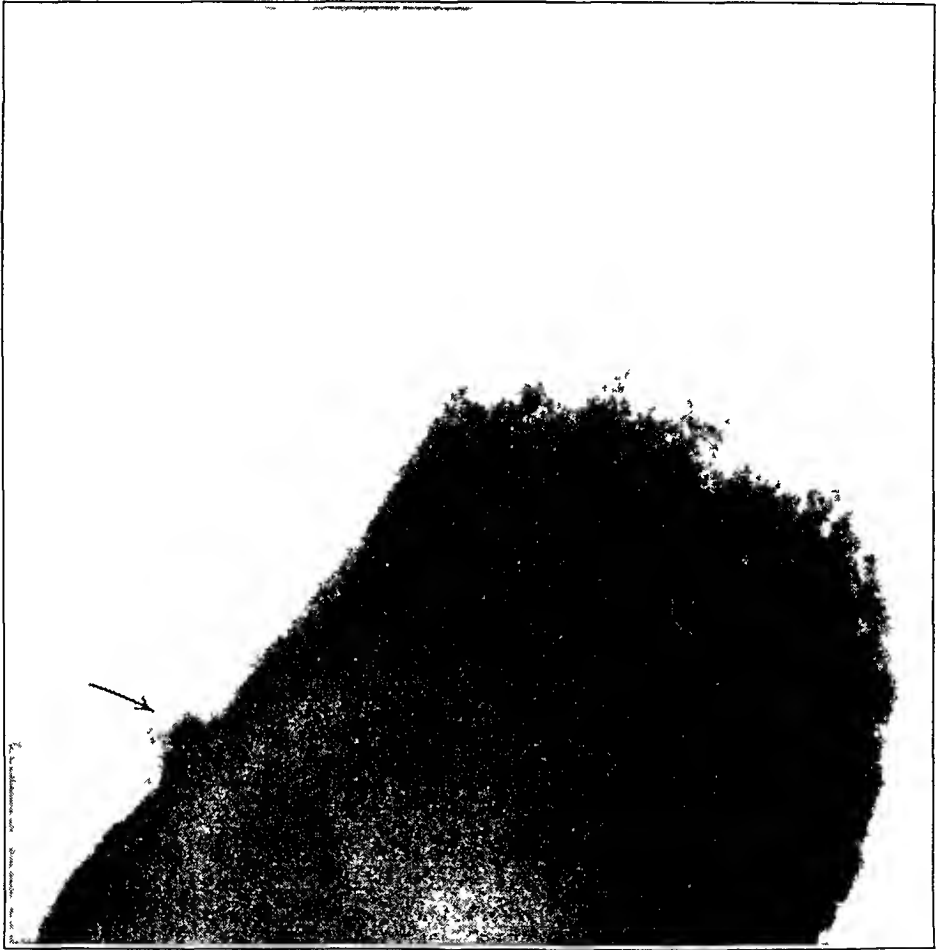


Fig. 1 (case 1).—Marked dilatation of the stomach due to obstruction at the outlet. The pyloric portion represented by the nipple-like projection has been drawn upward as a result of cicatricial shortening of the lesser curvature. The esophagus is normal.

mouth and pharynx. After the use of bland mouth washes and demulcents, the patient's symptoms disappeared. On June 12, 1928, he was discharged with instructions to return for observation and a warning of the possibility of gastric sequelae.

The patient reentered the hospital on July 2, 1928, with the complaint of constant gastric pain, acid eructations, vomiting and constipation. On examination, the epigastrium was prominent and tender and the borders of the stomach

easily outlined. Aspiration of the fasting stomach yielded 600 cc. of gastric contents which contained no free and 40 degrees of total acidity. The following morning, after an Ewald test breakfast, 650 cc. of material was removed with no free and 36 degrees of total acidity. Roentgenographic examination (fig. 2) demonstrated a normal esophagus and cardia. The pylorus was rigid, narrow,



Fig. 2 (case 2).—Anomalous deformity of the pyloric region and lesser curvature of the pars media due to acid corrosion. No roentgen evidence of abnormality of the esophagus is present.

deformed and elongated to measure more than 3 cm. Three small pockets protruded from the side of the lesser curvature in the distal portion of the stomach. The roentgenologic diagnosis of carcinoma of the pylorus was made with the reservation that a benign ulcer with extensive scarring might explain the roentgenographic appearance.

Laparotomy was performed by Dr. Karl A. Meyer, whose operative report reads: "The pyloric portion of the stomach is stenosed by a stricture which extends from a point 3 cm. proximal to the pylorus to involve the sphincter. There is scarring and puckering of the serosa over the pyloric region reaching for a distance of 6 cm. along the lesser curvature. The gastric mucosa is thickened, friable and bleeds easily." A posterior gastro-enterostomy was performed. Convalescence was uneventful, and the patient was discharged three weeks later, completely relieved of symptoms. The roentgenogram taken before discharge showed an adequately functioning gastro-enterostomy.

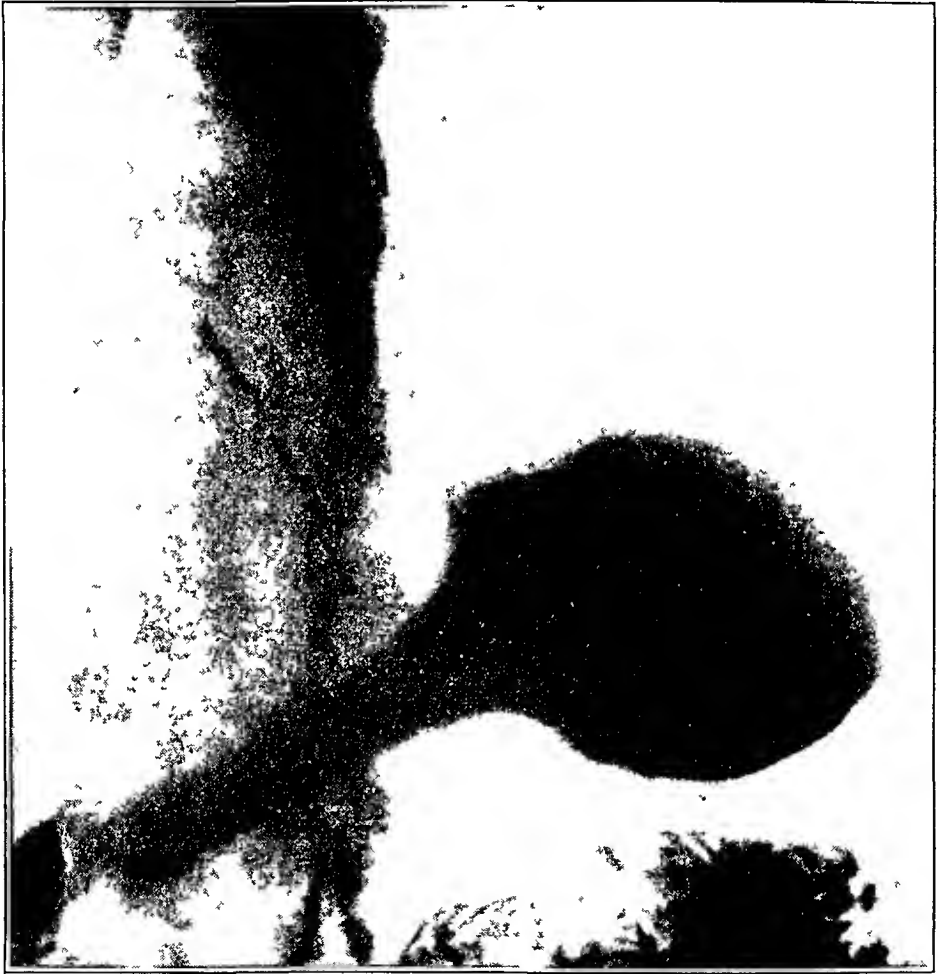


Fig. 3 (case 3).—Concentric cylindric stenosis of the distal two thirds of the stomach following corrosive poisoning. The barium within the esophagus is due to gastric regurgitation.

CASE 3.—A. S., a robust white man, aged 57, entered the hospital on March 8, 1929. He stated that twenty-four hours prior to admission, as he was about to return home for his evening meal, he swallowed a liquid which tasted like acrid wine and which was offered to him as whisky. Immediately after swallowing the fluid, the patient experienced severe epigastric pain and numbness in the region of the mouth and pharynx. Severe vomiting ensued, which became bloody within a short time. General weakness associated with a cold sweat followed. The patient then drank a bottle of milk, which he quickly vomited. On entrance,

his complaints were pain in the epigastric and retrosternal regions and sore throat. On examination, the mucosa of the mouth, uvula and pharynx was seen to be covered by a white membrane which in places was ulcerated and hemorrhagic. The temperature was 102 F., the pulse rate 110, and the respiratory rate 25. The patient was given milk to drink, whereupon retching and vomiting occurred. The vomitus was sanguineous. Sedatives and mineral oil were administered and a cocaine spray prescribed to control the pain in the pharynx. The patient improved rapidly and expressed a desire to leave the hospital. He was informed of the frequent sequelae, both esophageal and gastric, and was advised to remain. He accepted the advice.



Fig. 4 (case 4).—Roentgen evidence of deformity of the duodenal cap and the pyloric zone resulting from ingestion of dilute lye on a full stomach.

On March 23, 1929, while under observation, he first complained of slight dysphagia. The difficulty in swallowing became progressively worse. On April 3, roentgenographic examination revealed an esophageal constriction just below the level of the cricoid cartilage and (fig. 3) a tubular constriction of the pars media and the pars pylorica of the stomach, with no peristalsis. Repeated esophagoscopic examinations showed a friable, polypoid mucous membrane which the esophagoscopist persisted in reporting as carcinoma. In view of the history and our previous experience with the polypoid hypertrophy and friability of the mucosa of the stomach shortly after corrosive poisoning, we were reluctant to

accept this diagnosis. A biopsy was therefore taken and a report of inflammatory hyperplasia returned by the pathologist. Esophageal dilatation readily overcame the subcricoid constriction observed in the roentgenogram, but nevertheless the patient complained of distress following ingestion of a moderate-sized meal. Consequently, small frequent feedings were prescribed, and the patient was ren-

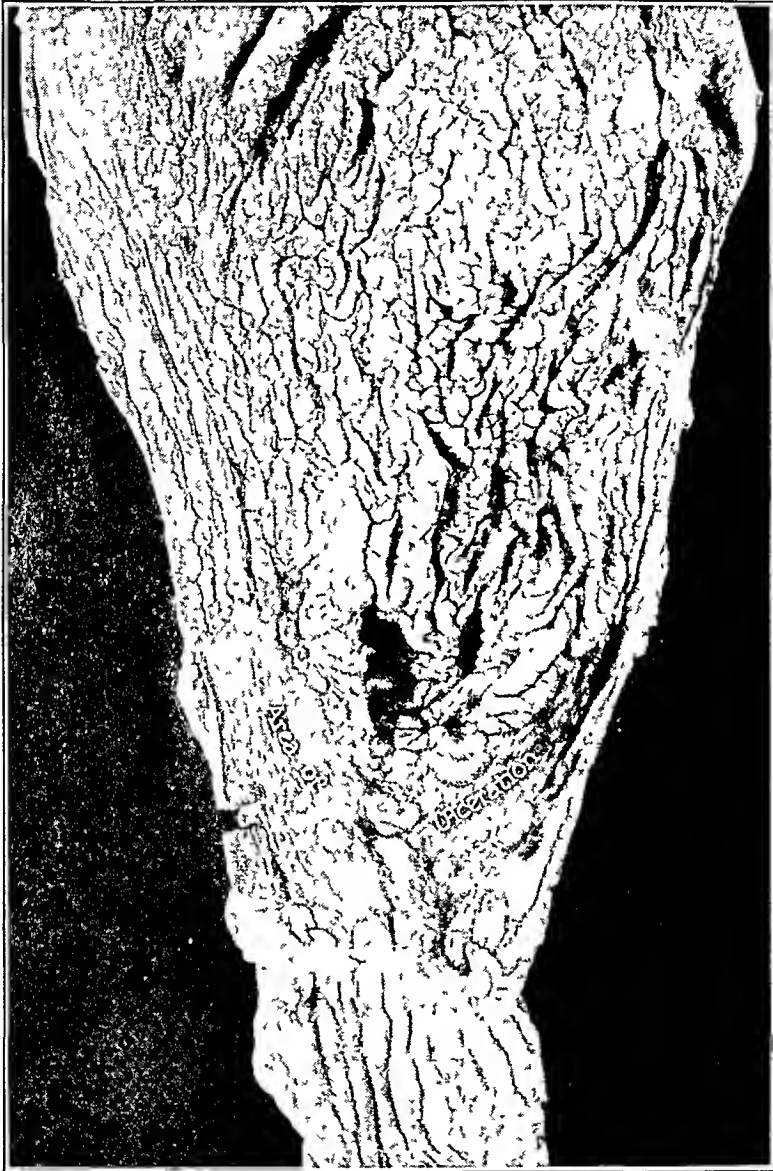


Fig. 5 (case 4).—Stomach and first portion of duodenum opened along the lesser curvature. Had the stomach been opened along the greater curvature, the area of ulceration would be seen to be triangular with the apex toward the cardia. Note the islands of remaining mucosa near the greater curvature.

dered practically symptom-free. He was discharged on June 26, 1929, approximately three and a half months after admission, with the advice to return on the slightest indication of further stenosis.

CASE 4.—E. B., a white man, 45 years of age, had been previously in good health but was unemployed and despondent. On July 11, 1929, he swallowed

half a tumbler of dilute lye in an attempt at suicide. He experienced severe epigastric burning, soreness of the throat and vomiting. The following day he entered the hospital, mainly on account of persistent emesis. On examination there were seen moderate injection and ulceration of the oral and pharyngeal mucosa. There was moderate epigastric tenderness. On treatment with liquid



Fig. 6 (case 5).—Atypical deformity of the pars pylorica consisting essentially of a filling defect and an addition shadow on the greater and lesser curvatures, respectively, due to acid corrosion.

petrolatum and a soft diet, the patient ceased vomiting and recovered satisfactorily. Roentgenographic examination (fig. 4) made on July 19, 1929, disclosed an irregular, rigid defect of the prepyloric, pyloric and duodenal regions, producing moderate obstruction. A roentgenologic diagnosis of carcinoma of

the stomach was made by the roentgenologist. This diagnosis was made despite the history, to which little credence was attached. On July 22, 1929, the patient committed suicide by hanging.

Through the courtesy of Dr. S. A. Levinson, the stomach and esophagus obtained at autopsy were placed at our disposal. Dr. Levinson's description is as follows: "The stomach has been opened along the lesser curvature (fig. 5). The esophagus and cardia are free from change. The rugae of the walls of the fundus and pars media and of practically the entire length of the greater curvature are normally prominent. The proximal two thirds of the lesser curvature is likewise practically normal, while in the distal third there is seen a triangular area of ulceration with the apex directed toward the cardia and the base ending abruptly just proximal to the pyloric ring. The stomach having been opened along the lesser curvature, the triangle is seen to be divided along its perpendicular. The area of ulceration is quite smooth, except for a few islands of mucosa which are retained, especially along the greater curvature side. The wall of the stomach in the involved area is firm and thick. The pyloric ring is thickened but free from ulceration."

Microscopic sections from the denuded area disclosed a complete loss of the mucosa and muscularis mucosae. There was a marked polymorphonuclear and round cell infiltration of the submucosa and muscularis. Sections from other parts of the stomach and from the esophagus showed no noteworthy change.

CASE 5.—D. B., a colored man, aged 33, was in good health until September 3, when, following a hearty evening meal, he drank approximately 4 ounces (118.29 cc.) of 12 per cent sulphuric acid, mistaking it for whisky. Immediately after drinking the acid, he hastened to the street, boarded a passing street-car, and after riding a few minutes experienced burning in the substernal and epigastric regions. He dismounted from the car, began to vomit, felt weak and fainted. He was brought to the Cook County Hospital, where he received gastric lavage and stimulants. He continued vomiting and suffering from epigastric pain for a few days, after which the pain disappeared. The vomiting, although it persisted, became less frequent and less profuse. The patient recovered his strength and at his request was released from the hospital on September 23, although he still experienced difficulty in retaining food.

He reentered the hospital on Oct. 1, 1929, complaining of persistent vomiting, epigastric cramps, weakness and loss of weight. From the history of an ingestion of acid on a full stomach, the presence of a pyloric obstruction due to cicatricial contraction was confidently predicted. The patient was given a glass of water, which he swallowed without difficulty and retained. The results of physical examination, except for epigastric tenderness, were negative.

Roentgenographic examination (fig. 6) on Oct. 3, 1929, showed an annular deformity of the pars pylorica of the stomach, which was rigid. The lesser curvature of the pars media was rigid and irregular. Operation performed the following day by Dr. V. L. Schragar revealed a contracted, thickened pars pylorica and an extensive fibrous perigastritis, especially along the lesser curvature. On account of the adhesions, the posterior wall could not be mobilized, and an anterior gastro-enterostomy was performed. The patient developed a subphrenic abscess which was surgically drained. A pyopneumothorax supervened and culminated in the patient's death. Autopsy was performed on Nov. 13, 1929, by Dr. J. J. Kearns, who demonstrated a tubular constriction of the pars pylorica and a high grade inflammation of the mucosa along the entire extent of the lesser curvature. There was no evidence of infection, old or recent, about the gastro-enterostomy site. The esophagus was normal.

COMMENT

In reviewing the cases described, one is struck by the uniformity in the sequence of events. The patient presents the symptoms and signs of recent corrosive poisoning, whereupon remedial measures are employed. The vomiting ceases more or less, the visible oral lesions disappear, and apparently the patient has recovered. As a consequence, he is discharged as cured or at least improved. Within a variable period, he returns with symptoms of obstructive vomiting, emaciation, and roentgen evidence of obstruction in the stomach alone or in combination with the esophagus. Although the clinical sequence of events is strikingly constant, the anatomic location and character of the lesions produced are variable. As will be seen later, the location and extent of residual involvement after corrosive poisoning are not purely accidental but are dependent on certain definite factors.

Factors Which Influence the Location and Type of Gastric Lesions.

—Type of Corrosive: The type of corrosive used, whether acid or alkali, has an important bearing on the localization of the permanent damage. The escape of the esophagus, with exclusive involvement of the stomach, is seen most frequently in cases in which acid has been employed. An explanation of this fact is furnished by the work of Delore and Armand.⁵ These authors showed that ordinary concentrations of acids during their rapid course through the esophagus have but a superficial scorching effect on the squamous epithelial lining. The simple columnar epithelium of the stomach is, however, readily corroded by similar concentrations of acids and this, combined with the longer duration of contact, leads to extensive damage. Lye, however, has a universally colliquative action, irrespective of type of tissue, so that esophagus and stomach are equally involved, the former more extensively, since dilution does not occur there. Orator,⁶ in an analysis of thirty-four cases of late gastric sequelae following the ingestion of acid, mentioned only seven cases in which combined pyloric and esophageal stenosis took place. In the remaining cases, gastric lesions exclusively were found. Rieder,⁷ Oeding,⁸ Liebman⁹ and others reported

5. Delore and Armand, quoted by Elisher, E.: Pylorusstenosen hervorgerufen durch Salzsäuren und Aetzlaugen, *Zentralbl. f. Chir.* **50**:165 (Feb. 3) 1923.

6. Orator, V.: Säurenverätzungen des Magens und Zinkdampfschaden, *Zentralbl. f. Chir.* **56**:514 (March 2) 1929.

7. Rieder, W.: Pylorus Stenose infolge Mineralsäureverätzungen, *Zentralbl. f. Chir.* **56**:1049 (April 27) 1929.

8. Oeding, H.: Ein Fall von Pylorusstenose nach Salzsäureverätzung, *Zentralbl. f. Chir.* **53**:397 (Feb. 13) 1926.

9. Liebman, E.: Ueber einen Fall von Abgang der Magenschleimhaut durch dem Darm nach Vergiftung mit konzentrierter Salzsäure, *München. med. Wchnschr.* **64**:1292 (Oct. 2) 1917.

only pyloric stenosis as following the ingestion of acids. With alkalis, on the other hand, gastric strictures, when they occur, do so as a rule in combination with esophageal stenosis, as in the cases described by Vinson and Hartman,² Rochet and Barbier¹⁰ and others. Heindl¹¹ in his review of 116 cases of stricture of the esophagus caused by lye found only 20 per cent associated with pyloric stenosis. Exclusive late involvement of the stomach after the taking of alkali is rare. A case described by Elisher¹² in which six months following the ingestion of lye only pyloric stenosis was found, and our case 4, in which the only demonstrable lesion was gastric, are worthy of note.

Concentration of Corrosive: The concentration of the corrosive does not play the important rôle one might expect. The highly concentrated poisons cause perforation and early death and therefore do not concern us here. In general, the alkalis are taken in the form of lye; the acids, in the commercially employed strengths. However, no concentration of corrosive, regardless of how dilute, is to be considered innocuous. It is particularly with low concentrations which have little or no effect on the esophagus and which are longest tolerated within the stomach, that extensive gastric changes are produced. Sick¹³ reported a case of pyloric stenosis following the ingestion of a small amount of dilute acid and demonstrated experimentally the importance of dilute corrosive in producing extensive gastric damage.

Location and Type of Lesion.—When a group of patients presenting late permanent changes within the stomach are studied, it is seen that the location and extent of the lesions vary. A pyloric stenosis, a tubular narrowing of the antrum and pylorus, an hour-glass constriction, concentric constriction of the pars pylorica and pars media, a leather bottle type of deformity or various combinations of these lesions are encountered. Again the scarring is thin or heavy, localized or universal, focal or diffuse. The different types of structural change are fully discussed by Merkel¹⁴ in his comprehensive treatise on the pathologic

10. Rochet, P., and Barbier, J.: Stenose cicatricielle oesophagienne et pylorique a la suite d'une ingestion de liquide caustique, *Lyon chir.* **24**:405 (July-Aug.) 1927.

11. Heindl D.: Klinische Beobachtungen an 137 gutartigen Oesophagusstenosen der I Chirurgische Universitätsklinik, Wien., 1901-1925, *Ztschr. f. Chir.* **199**:252 (Nov. 1) 1926.

12. Elisher, E.: Pylorusstenosen hervorgerufen durch Salzsäuren und Aetzlaugen, *Zentralbl. f. Chir.* **50**:165 (Feb. 3) 1923.

13. Sick, K.: Klinische, experimentelle und histologische Untersuchungen über Säurevergiftung des Magens, *Deutsches Arch. f. klin. Med.* **148**:318 (Oct.) 1925.

14. Merkel, H.: Die Magenverätzungen, in Henke, T., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 4, pt. 1, pp. 219-315.

anatomy of corrosive action on the stomach. The question naturally arises, what determines the localization and extent of the defect which affects the stomach? The explanation involves a knowledge of the physiology of gastric reception of food and fluids.

As early as 1905, Grützner¹⁵ demonstrated by means of various colored foods that within the fundus stratification and storage occur. Cohnheim¹⁶ in 1907 demonstrated the rapidity with which fluid ingested on a full stomach appears almost unchanged in the duodenum tapped by an artificial fistula. Later Waldeyer¹⁷ and Aschoff¹⁸ presented the idea of a "Magenstrasse," a conception according to which the lesser curvature acts as the pathway for rapid progress of fluid from the esophagus to the pylorus without the admixture of food and also as the passageway for well triturated food from the stomach into the duodenum. The work of Waldeyer and Aschoff furnished a logical basis for Grützner's¹⁵ and Cohnheim's¹⁶ observations and also an explanation for the type and localization of gastric lesions following corrosive poisoning.

In the full stomach, the ingested corrosive fluid is rapidly passed through the esophagus along the lesser curvature to the pylorus where it spreads out in triangular fashion with the base toward the pylorus and the apex toward the cardia (see fig. 5). There occurs a pylorospasm which halts the further progress of the fluid, and the contraction of the stomach renders the lesser curvature very short. The corrosive is in contact with the mucosa of the pylorus and lesser curvature on the one side and with food on the other. The latter has diluting and neutralizing effects. Within a short interval, vomiting takes place, ridding the stomach of the corrosive, but leaving a raw ulcerated lesser curvature and pars pylorica where toxic and perhaps bacterial gastritis may supervene. The predetermined strictural changes are stenosis of the pylorus with scarring of the lesser curvature and some degree of antrum involvement (figs. 1, 2, 4 and 6). With acids, these changes occur alone; with alkalis, usually in combination with esophageal strictures.

In the empty contracted stomach, on the other hand, the lesser curvature is almost vertical, and the stomach forms a funnel (Kaufmann¹⁹) with the antrum and pylorus constituting the deepest portions.

15. Grützner, P.: Ein Beitrag zum Mechanismus der Magenverdauung, Arch. f. d. ges. Physiol. **106**:463 (Feb.) 1905.

16. Cohnheim, O.: Beobachtungen über Magenverdauung, München. med. Wchnschr. **54**:2581 (Dec. 24) 1907.

17. Waldeyer, W.: Die Magenstrasse, Sitzungsber. d. k. Preuss. Akad. d. Wissensch. **29**:595, 1908.

18. Aschoff, L.: Ueber den Engpass des Magens, Jena, Speyer & Kerner, 1908.

19. Kaufmann, E.: Spezielle pathologische Anatomie, ed. 7 and 8, Berlin, W. de Gruyter & Company, 1922, vol. 1, pp. 529-533.

The ingested liquid comes in universal contact with the gastric mucosa, but remains longest in contact with the pars pylorica and pars media because pylorospasm prevents further progress onward of the corrosive, while the air above the fluid diminishes the extent of contact with the fundus. Hence, although vomiting occurs much earlier with the empty than with the full stomach, dilution and absorption of the corrosive and protection of the mucosa by food are absent. As a result extensive ulceration and damage occur. If perforation and death do not ensue, there results complete pyloric and antrum constriction, with simultaneous narrowing of the pars pylorica and pars media (fig. 3), total gastric scarring (linitis plastica) or hour-glass stenosis due to antrum spasm.

Actual data as to the condition of the stomach, whether full or empty prior to the ingestion of the poison, are meager. Although many authors (Shinz,²⁰ Elisher,¹² Merkel,¹⁴ Galdau and Pop²¹ and others) emphasized the importance of the state of the stomach, only few offered specific information with reference to this point. Elisher¹² recorded the condition of the stomach in his own cases and suggested the view expressed here. In cases 1, 2 and 5 of our series, the corrosive was swallowed after eating, and in each case a pyloric stenosis with scarring of the lesser curvature resulted. The patient in case 3 ingested the poison on an empty stomach just before going home for his evening meal; in this case, extensive constriction of the pars pylorica and pars media was produced. In case 4, no information was recorded regarding the state of the stomach at the time the lye was ingested. From the type of lesion produced it is reasonable to assume that the stomach was empty.

Clinical and Roentgenographic Aspects of Gastric Sequelae of Corrosive Poisoning.—The interval that elapses between the ingestion of the corrosive and the development of the gastric stricture is variable. The usual period is from one to six months. According to published reports, the time interval most frequently is from three to four weeks, as occurred in most of our cases. The gastric sequelae may not, however, progress to the point of giving symptoms for several years after the swallowing of the poison. Thus Galdau and Pop²¹ cited two instances of the ingestion of alkali in each of which an early esophageal constriction was overcome by dilatation, with apparent recovery, but was followed in three years in one and in six years in the other case by vomiting. Roentgenograms revealed obstructive deformities of the

20. Shinz, H. R.; Baensch, W., and Friedl, E.: *Lehrbuch der Roentgendiagnostik*, Leipzig, 1928, pp. 926-927.

21. Galdau, D., and Pop, A.: *Die postkaustischen Magenverätzungen*, *Fortschr. a. d. Geb. d. Roentgenstrahlen* **37**:705, 1928.

antrum and pylorus in both patients. Assmann²² reported a case of pyloric stenosis which occurred nine years after corrosive poisoning.

The two cases of Galdau and Pop, as well as one described by Orator,⁶ illustrate an interesting series of events. The initial symptoms of corrosive poisoning may be followed after an interval by evidences of obstruction of the esophagus or cardia. Following relief of the esophageal or upper gastric stricture, another obstruction, lower in the stomach, may develop. Orator described a case of stenosis of the cardia which followed one month after the ingestion of hydrochloric acid and for which gastrostomy was performed. The result was satisfactory for eight days; then regurgitation through the fistula made it evident that a pyloric stenosis had supervened. A jejunostomy performed for relief ended fatally.

The clinical picture presented by the gastric sequelae varies only in detail. Epigastric pain and vomiting are universal. The pain is usually mild, and is dependent on the disturbance in motility. A sense of pressure and fulness after meals, relieved by vomiting, is most frequent. At times, especially with lesser grades of obstruction, epigastric cramps of moderate severity are experienced. Vomiting is by far the most obtrusive and most persistent symptom. It follows immediately to several hours after the taking of food. The vomitus may contain, in addition to undigested food, blood, pus, lactic acid and Oppler-Boas bacilli. Hydrochloric acid is generally absent or if present is low in amount, as in case 1 of our series. The secretory and motor disturbances produced by corrosives may be maintained, as emphasized by Sick,¹³ over a long period of time. This investigator, although unable to reproduce strictures in his animals, noted decreased motility and secretion for months after the corrosive was administered.

The patient presents physical evidence of emaciation and dehydration of varying degree. The abdomen may be scaphoid, but frequently the stomach produces an epigastric fulness due to gastric tonicity or distention with at times visible peristalsis. Even in cases in which a concurrent esophageal stenosis exists, providing it is incomplete, prominence of the epigastrium with peristaltic waves may be seen rather than the expected scaphoid abdomen. This paradoxical combination of esophageal obstruction and gastric distention was first described in a case reported by Rochet and Barbier.¹⁰

From the clinical data alone obstruction high in the gastro-intestinal tract is readily diagnosed. The roentgenogram employed for more accurate diagnosis reveals a variety of structural and functional changes.

22. Assmann, H.: *Klinische Roentgendiagnostik der inneren Erkrankungen*, ed. 3, Leipzig, F. C. W. Vogel, 1924, pp. 473-475.

Pyloric stenosis, pyloric and antral constriction, rigid cylindric narrowing of the pars pylorica and pars media, hour-glass constriction or total gastric contraction, alone or in combinations or in association with esophageal strictures, is encountered.

Deformities of the stomach resulting from corrosive poisoning as shown by the roentgen ray are often mistaken for other lesions, particularly for carcinoma and ulcer. The summaries of Galdau and Pop²¹ of eight of their own cases and thirteen from the literature illustrate the difficulties in radiologic diagnosis. These authors described particularly one case in which pain and vomiting led to a roentgen examination, which revealed a rigid, narrow antrum and pylorus. A roentgenologic diagnosis of carcinoma was made. The deformity, however, was due to cicatricial contraction occasioned by the ingestion of alkali six years prior. Schinz²⁰ and Assmann²² mentioned similar experiences. In case 1 of our series, the roentgen diagnosis of ulcer with stenosis was made, and in cases 2 and 4 the roentgen interpretation was gastric carcinoma. Differentiating features mentioned by various authors, such as the greater delicacy and more linear contour of the corrosive lesions, may be of some help, but generally are not dependable. Multiplicity of lesions, on which the correct diagnosis was based in case 3, is highly suggestive.

The changes in motility as observed roentgenologically are also variable. A review of the recorded observations and of our own shows that all variations occur, from huge, atonic dilated stomachs with absence of peristalsis, as in case 1 of our series, to small, contracted stomachs with hypermotility, as in case 3. Spasm at the site of injury especially early is a prominent feature, as demonstrated by Liebman,⁹ who roentgenologically followed a case of poisoning throughout its course. He found a sickle-shaped, contracted stomach five days after ingestion of the corrosive, which later resumed the normal gastric outline, except in the region of the pylorus, where permanent stenosis occurred.

A consideration of the roentgen appearances of the gastric sequelae of corrosive poisoning points to the conclusion that the history is of utmost importance in arriving at a roentgenologic diagnosis. The difficulty of distinguishing a cicatricial from a neoplastic deformity on the basis of the roentgen observations alone and the influence which the anamnesis exerts on the roentgenologist's opinion are exemplified by the following case:

On May 19, 1929, a colored man, 38 years of age, ingested what was alleged to be lye and immediately afterward experienced severe abdominal pain. He vomited a clear material after a few minutes. This was followed by frank blood. About one hour later, the hematemesis was repeated in the hospital examining-room. He was sent to the roentgenologic department with a definite diagnosis

of corrosive poisoning. The roentgenogram, taken June 16, 1929, showed an irregular filling defect of the prepyloric region with obstruction. The roentgen diagnosis was corrosive cicatrization of the prepyloric area. The exploratory operation revealed an extensive carcinoma of the prepyloric region involving also the perigastric lymph glands. Subsequent investigation disproved the original history and showed that the material ingested was milk of magnesia.

Treatment.—The treatment of gastric sequelae is usually surgical. Occasionally, the medical management succeeds, particularly in cases in which the obstruction is due wholly or in part to spasm or active inflammatory processes which recede. Sick,¹³ for instance, treated a patient with corrosive pyloric stenosis for six months expectantly, and recovery ensued without operation. The type of operation may vary according to the time that elapses following the initial accident. In the late cases, gastro-enterostomy is the operation of choice. In the early cases, Rieder,⁷ among others, advises preliminary jejunostomy to permit the stomach to rest and the gastritis to subside. Our experience with case 5 supports the idea that gastro-enterostomy in the presence of an active inflammation may prove disastrous and should be postponed. Combination stenoses present special problems.

(CONCLUSIONS

1. The ingestion of acid even in relatively small quantities or low concentrations may be followed by stenosis of some part of the stomach without esophageal involvement.

2. The swallowing of lye leads to esophageal obstruction associated frequently with gastric obstruction, rarely to gastric obstruction alone.

3. Organic obstruction of the stomach does not occur immediately, but usually manifests itself several weeks after recovery from the initial effects has been considered complete.

4. Late gastric stenosis should be anticipated in all cases of corrosive ingestion (especially when the substance is known to be an acid), even though the patient is restored to complete health shortly following the poisoning.

5. The type and location of the lesion in the upper part of the gastro-intestinal tract can be predicted from a knowledge of the corrosive ingested, whether acid or alkali, and the state of the stomach, whether empty or full.

6. In late cases of cicatricial stenosis of the stomach, gastro-enterostomy is the operation of choice. In early cases in which an active inflammation exists, a preliminary jejunostomy is often advisable.)

Book Reviews

HYPERTENSION AND NEPHRITIS. By ARTHUR B. FISHBERG, M.D., Adjunct Attending Physician to Mount Sinai and Montefiore Hospitals, New York. Price, \$6.50. Philadelphia, Lea & Febiger, 1930.

This book is intended for the general practitioner, yet it is undoubtedly the best work in its field in English, not only from a practical clinical standpoint, but as a clear, critical, extremely well balanced digest of the literature on the many pressing problems of Bright's diseases. The author has contributed personally, in no small degree, toward the solution of some of these problems so that one appreciates, all the more, the direct frankness with which he disposes of the chaff and the unnecessary tags and ends passing ordinarily as scientific work. The chief aim of the author seems to be simplicity, whether he is discussing renal function tests, pathology, classification of Bright's diseases or treatment. Nowhere, however, does this simplicity replace the completeness of important details. It consists largely in the careful separation of essentials from nonessentials. Hence the book is a true quintessence of all the important factual and theoretical content of our knowledge of Bright's diseases.

The title at once indicates the author's credo—"Hypertension and Nephritis"—two separate groups of diseases, yet somehow interrelated. The arrangement is admirable, proceeding from a discussion of disturbed renal function and its consequences to tests of renal function, the four cardinal aspects of Bright's diseases—albuminuria (and cylindruria), edema, uremia and arterial hypertension with all its sequels—and the subdivisions of Bright's diseases, i. e., the nephroses, nephritides and essential hypertension. The large apportionment of space to acute glomerulonephritis and to essential hypertension seems very wise in view of the keystone positions of these two conditions.

The author constantly stresses the unitary nature of impairment of renal function, that is, the loss of concentrating power regardless of the substance considered. Cushny, Starling and Richards are not mentioned in the chapter on pathologic physiology. Is the gap between the normal and pathologic physiology of the kidneys completely unbridgable? Most of the renal function tests, including metabolic balance studies, are shown to be unnecessary or useless while the author's simplified concentration or specific gravity test is preferred for clinical work. The distinction between renal impairment detectable by concentration tests and renal insufficiency as shown by nonprotein nitrogen retention in the blood is clearcut. The author describes in detail the urea clearance test of Van Slyke and his associates but fails to understand the difference between it and the Ambard constant, and questions its superiority over his own test without giving any comparative studies. The simple specific gravity test, however, may be easily carried out by the general practitioner and can give him a surprisingly accurate index of renal function.

Albuminuria is attributed to glomerular changes rather than to biologic alteration of the plasma proteins. Nephrotic edema is explained on the mechanical basis so richly supported by the clinical and experimental work of the last thirty years. The author's review of this work is brief but masterly. Acute nephritic and cardiac edemas are properly separated out. A primary rôle of the tissues in edema is ruled out on the grounds of lack of convincing evidence. The treatment for edema includes the best available information, stripped of all encumbrance. Nowhere in the literature on edema will a better chapter than this one be found.

Uremia is defined as a complex autointoxication resulting from the summation of the effects of retention of the various urinary constituents. The clinical picture is clearly delineated, the diagnosis made precise and the treatment sanely grounded.

In the chapter on arterial hypertension emphasis is laid on the relative nature of normal blood pressure and the factors underlying it. The pathologic anatomy

of hypertension is a field peculiarly the author's own province and is admirably sketched. Throughout this part precise definition of pathologic concepts is resorted to, thus making a complex subject much more intelligible. The unique distribution of arteriosclerosis in various organs, the lack of evidence of the systemic nature of this process, the relationship to age and the rôle of this vascular disease as a sequel to hypertension are some of the important items discussed. The mechanism of cardiac dilatation and insufficiency is frankly admitted to be unknown. The pathogenesis of arterial hypertension is exhaustively considered. The author leans toward the teleologic theory of renal hypertension and the concept of widespread functional vasoconstriction in all forms of hypertension of long duration. He contradicts himself somewhat on page 189, when speaking of hypertension as only a symptom and later of essential hypertension as a disease. Hypertensive encephalopathy is very well discussed from every angle. It is clearly separated from true uremia and closely related to eclampsia and lead encephalopathy. Cerebral vascular spasm is given the leading rôle, with edema a secondary and inconstant position. Hypertensive retinitis is adequately described except for insufficient analysis of the relationship of retinal arteriosclerosis to the ophthalmoscopic observations.

The classification of Bright's diseases is essentially a modernized version of the Volhard and Fahr system, with substitution of essential hypertension for benign and malignant nephrosclerosis and inclusion of benign albuminurias, multiple glomerular embolization and the senile arteriosclerotic kidney in individual rubrics.

The nephroses are defined from the original anatomic point of view and then subdivided. Mercurial nephrosis is briefly but sufficiently reviewed. The subject of chronic nephrosis is skilfully treated. The sequence of albuminuria, reduced plasma proteins, edema and lipemia is developed with perfect clarity. A combination of the renal and metabolic theories of pathogenesis is favored, with the interesting suggestion that nephrosis may be a collective concept for several distinct diseases. The treatment for chronic nephrosis, as detailed by the author, can scarcely be improved.

The important subject of acute glomerulonephritis is exceedingly well treated. The discussion of etiology, pathology and pathogenesis is second to none in the literature. The author differentiates sharply between diffuse and focal forms. The clinical picture is complete. The treatment meets each indication squarely and disposes of many outworn notions.

Chronic glomerulonephritis is logically developed from the acute type and given the same thorough analysis. The anatomic picture is enriched by the author's experience with the various types of arterial lesions. The variegated clinical features stand out distinctly to give an actual concept of the disease as a whole. Treatment, again, is splendidly considered. Throughout, the author's clinical maturity and sound judgment predominate.

Essential hypertension is admitted as a cloak for ignorance in analogy with the old term "pseudoleukemia." The pathology secondary to hypertension is, as usual in this book, excellently outlined. The "malignant phase" is defined on the basis of arteriolonecrosis and endarteritis and acutely progressive renal insufficiency. If accepted, this definition should materially reduce the clinical incidence of malignant hypertension. The gross and microscopic picture of the malignant phase is excellently portrayed. In further chapters the various factors involved or claimed to be important in the pathogenesis of hypertension are discussed. Endocrine etiology is ruled out except in the case of the suprarenal tumors, and even there the mechanism is still in the realm of mere speculation. "There are few fields in medicine in which ignorance is more profound," p. 441. High protein diet is discarded as a significant cause. Obesity, gout, alcohol, salt, tobacco, cholesterol, intestinal intoxication, etc., are all put in their proper place—the first two as constitutional associates of hypertension and the rest as hard-ridden medical hobbies. Emotional and mental factors are not credited with the capacity of causing hypertension but are considered important accessories. On the whole, according to the author, an inherited constitutional predisposition is the fundamental basis of essential hypertension. It takes courage to state that no effect was ever seen on the

blood pressure from the removal of infected teeth, tonsils or other foci of infection. The whole clinical syndrome, with the important cardiac manifestations—including angina pectoris and cardiac asthma, the nervous symptoms, renal function, the changes in the eyegrounds, etc.—are all thoroughly and accurately rendered. Diagnostic difficulties are met and defeated. Prognosis is given. The treatment is at the same time ancient and modern; ancient in its philosophy of “moderation in all things” and modern in its meticulous detail. Nothing of value has been left out; nothing irrational has been included.

Finally, comes a rather sketchy discussion of renal and hypertensive disease in pregnancy, a field obviously not within the author's own experience. This chapter is somewhat of an anticlimax.

Minor errors in typography and the spelling of authors' names will undoubtedly be corrected in future editions. The illustrations are satisfactory. This book by Fishberg meets the crying needs of the practicing physician, the medical student and the clinical teacher and investigator. It is a landmark in American medical publication.

DIAGNOSTISCHE UND THERAPEUTISCHE IRRTÜMER UND DEREN VERHÜTUNG—
INNERE MEDIZIN; ERSTES HEFT, KRANKHEITEN DES STOFFWECHSELS.
ZWEITE, VOLLKOMMEN NEU BEARBEITETE AUFLAGE. VON PROFESSOR DR.
S. ISAAC, Dirigierender Arzt der Inneren Abteilung des Krankenhauses der
Israelitischen Gemeinde in Frankfurt a. M. Price, 10 marks. Pp. 150.
Leipzig: Georg Thieme, 1929.

A condensed but complete and readable review of certain metabolic diseases is presented in this second edition under the title given. Of the conditions dealt with by the author, obesity and diabetes mellitus are given the largest amount of space and by far the best handling. From the point of view of the general practitioner, to whom the book is addressed, it would be difficult to find a saner or more helpful discussion of the theoretical and practical problems involved in the diagnosis and treatment of obesity and diabetes mellitus. Undernutrition, diabetes insipidus and gout are also taken up. The large clinical experience of the author and his familiarity with the literature, combined with good judgment in therapeutics, make this book a valuable reference for the practicing physician. Translation into English would seem desirable.

HANDBUCH DER ERNÄHRUNGSLEHRE. BAND II: SPEZIELLE DIATETIK DER
KRANKHEITEN DES VERDAUUNGSAPPARATES. TEIL I: MAGEN. By CARL
VON NOORDEN, Frankfort-on-Main and HUGO SOLOMON, Buenos Aires.
Price, 39 marks. Pp. 460. Berlin: Julius Springer, 1929.

This is a portion of an encyclopedia of clinical medicine compiled by Langstein, von Noorden and Schittenhelm. It is typically German in its thoroughness. If one desires a reference book wherein one may find a consideration of all treatments ever recommended for any gastric condition, this work fills the requirement. It is complete. For any other purpose, however, such a compilation is of little value. The treatment of gastric disorders is neither as complicated nor as difficult as this volume would indicate. The known facts of gastric therapy as related to recognizable gastric disease could be given in fewer pages.

THE BABY'S FIRST TWO YEARS. By RICHARD M. SMITH, M.D. Price, \$1.75.
Pp. 159, with illustrations. Boston: Houghton Mifflin Company, 1930.

This manual answers the majority of questions that perplex the young inexperienced mother in the care of her baby. It is brief, clear and well written.

The first part deals with the development of the baby, breast and bottle feeding, the care of the body, habits and training and clothing. One chapter is devoted to the sick baby. In the second part, the baby's entire daily routine is outlined in minute detail and offers a great many valuable suggestions.

The third part is devoted to charts for recording the baby's progress, and a few simple recipes are given.

Among the many books written for mothers on the care of infants, this ranks among the best.

DIGESTION

EFFICIENCY WITH VARIOUS FOODS AND UNDER VARIOUS CONDITIONS *

JOHN H. CHILDREY, M.D.

Fellow in Otolaryngology, the Mayo Foundation

WALTER C. ALVAREZ, M.D.

AND

FRANK C. MANN, M.D.

ROCHESTER, MINN.

The studies here reported represent a continuation and an amplification of those published by Hosoi, Alvarez and Mann.¹ We wondered if we could improve intestinal absorption by dividing the food into a number of portions and giving the portions at intervals, and we thought it might be helpful to mince the food or to slow the progress of peristalsis with morphine. We wondered also what would be the effect of giving progressively larger amounts of foods. Would the efficiency of digestion fail gradually at a certain point or would it break suddenly?

METHOD OF EXPERIMENTATION

As was reported by Hosoi, Alvarez and Mann, the colon was removed from three dogs, and the distal end of the ileum was joined to the stump of the rectum. In this way digestion in the small intestine could be studied in animals that were free from the soiling and irritation of the skin which is inevitable with an ileal fistula. These dogs, after being used for the experiments already reported, were kept about the laboratory for almost a year. It was then found, with the help of the roentgen ray, that some hypertrophy had taken place in the rectal segment. This was most marked in one animal (the third dog) in which at operation more of the rectum had to be left than in the others. This hypertrophy of the rectal segment probably accounts for the fact that with certain foods the fecal residues of these dogs are somewhat different now from what they were a year ago. As one would expect, the largest difference was observed in the third dog, in which there is now an almost normal rectum.

* Submitted for publication, Feb. 28, 1930.

* From the Division of Medicine, the Mayo Clinic and the Division of Experimental Surgery and Pathology, the Mayo Foundation.

1. Hosoi, Kiyoshi; Alvarez, W. C., and Mann, F. C.: Intestinal Absorption: A Search for a Low Residue Diet, *Arch. Int. Med.* **41**:112 (Jan.) 1928.

The accompanying table shows, for the first three dogs, the difference in the amount of feces (formed during a twenty-four-hour fast) obtained by Hosoi in 1927 and by us a year later when the remnant of colon had hypertrophied. It shows how much of the fasting fecal material is contributed by the colon. It is worth noting, however, that even in the animals with a small remnant of colon the discharges had almost no fecal odor.

At the beginning of this study three new dogs were operated on. In one, almost complete colectomy was done, while in the other two, ileostomy was performed a short distance above the ileocecal sphincter. The animal from which the colon was removed was a poodle weighing 4.9 Kg.; one dog was a fox terrier which weighed 7.6 Kg., and the other was a poodle which weighed 6.2 Kg.

In order to collect the fecal residue from the animals with an ileal fistula, an attempt was first made to strap a cup over the opening, but this apparatus did not work well and it had to be abandoned. The

Moist Weight of Discharges Recovered During a Twenty-Four-Hour Period of Fasting

Dog	A Few Weeks After Operation, Gm.	Ten Months After Operation, Gm.
First	6.8	8.3
Second	9.9	24.0
Third	15.6	42.0

dog was kept loosely restrained in a wooden frame, in which he usually slept for the eight-hour period of observation. A receptacle placed on the floor under the fistula caught everything that was passed. The other dog with the fistula was easier to handle when kept in a metabolism cage.

The dogs on which colectomy had been done were easier to work with than those with ileostomy. They were cleaner and more easily cared for, and it was easier to keep them in a good state of nourishment. There was little difference in the amount of fecal residue obtained from the dogs with the two types of operation.

It was found that in the three dogs originally used by Hosoi, feces could no longer be removed easily with the help of the tube which he devised; so these dogs also were kept in metabolism cages, and at the end of every hour the material passed was collected from the pan.

The dogs were fed weighed amounts of food at 8:30 a. m. Some of the less palatable foods had to be given by stomach tube. As the feces were passed, they were weighed moist, and the figures were plotted as cumulated percentages of the amounts fed. Water was not given during the eight-hour period of observation. When we were studying food which we knew would not be digested for a long time, the dog was made

to fast for twenty-four hours after the meal, so that when the next experiment started the bowel would surely be empty.

In all six dogs it was found that the taking of food was followed in a few minutes by the extrusion of a small amount of material from the bowel. This movement was probably brought about by the so-called ileocolic reflex which has been described by a number of writers. In another half hour there was generally another small movement which consisted of residues of the meal from the day before. In the dogs with an ileostomy opening, the next bowel movement usually occurred about two and a half hours after the taking of food, and in those which the colon was excised, the interval more often was from three to five hours. When liquid food was taken, this interval was usually somewhat shortened. After this, the fecal residue continued to appear at fairly frequent intervals for six hours longer. Movements were seldom seen after nine hours. On one occasion it was noted that it took seventeen hours for a chicken bone to pass.

In these experiments we have used as an index to the efficiency of digestion the percentage relationship between the moist weight of the feces and the moist weight of the food. It would have been more satisfying to deal with dry weights, but the work of Hosoi, Alvarez, and Mann revealed so little difference in the water content of feces obtained with different diets that, for the purposes of this study, we thought it hardly necessary to go to the extra labor of drying the foods and the residues.

EXPERIMENTS WITH DIFFERENT FOODS

Milk.—We confirmed Hosoi's observation that most of the residue from milk is passed within a few hours. Large amounts of milk were given in an attempt to overwhelm the digestive tract. Sometimes we gave as much as 90 Gm. for each kilogram of body weight. In a few instances undigested curds were passed, but there was never any change in the type of curve obtained, or any increase in the percentage of residue excreted.

Sour milk was better digested than sweet milk. The residues from the former amounted usually to from 18 to 25 per cent and from the latter to from 33 to 54 per cent.

Hosoi found that the addition of bread to milk tended to decrease the percentage of moist residue obtained. These results were confirmed, and it was found that other foods such as meat, raw egg, potato, and Karo syrup, when added to milk, also tended to decrease the amount of residue obtained. Similarly, the residue obtained after feeding bread was often diminished by the addition of milk to the ration, even when large amounts of the fluid were used. There was no reduction, however, when evaporated milk was added; this somewhat increased the amount of residue. The weights of the residue from meat and potato were not materially altered by the simultaneous giving of milk.

Lactose.—Hosoi called attention to the purgative action of lactose. When added to farina it increased the amount of residue obtained. These experiments were repeated and the observations confirmed (chart 1). Lactose was given in a 25 per cent solution and also in the form of

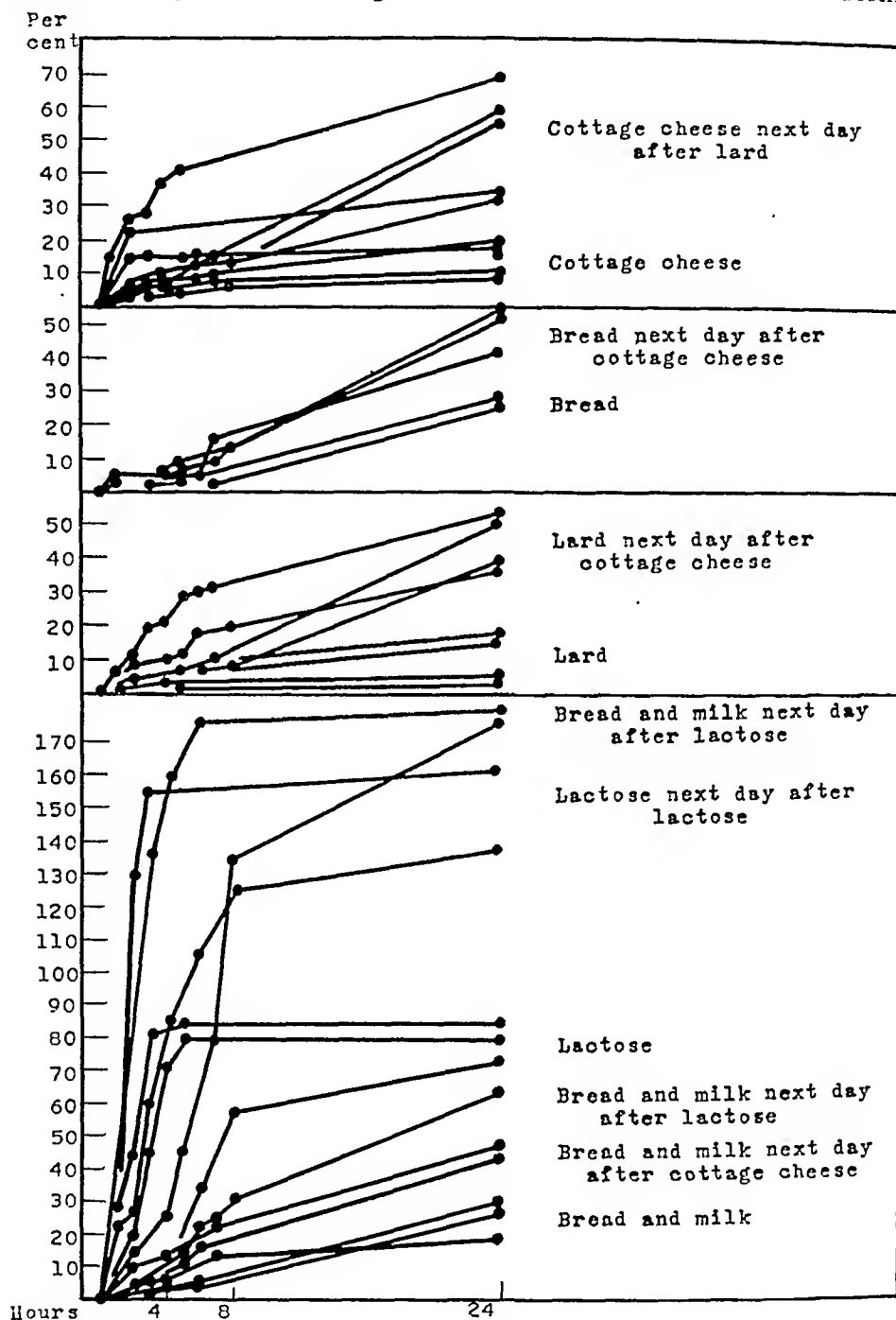


Chart 1.—In this and all subsequent illustrations abscissas represent hours after feeding and ordinates represent amounts of residue expressed as cumulated percentages of amounts of food given. Lines connect data obtained in one experiment. Data presented in this chart show that certain foods given one day can influence adversely the digestion of others given the following day.

powder. The substance had a cathartic effect, and when it was given repeatedly on successive days, the bowel became increasingly irritable. On days following the administration of lactose, any food that was given went through the bowel more rapidly than normal and the amount digested was lessened. The animals did not seem to feel well, and they showed little inclination to eat. These observations agree with those of Mitchell² and Evans and Burr³ who found that rats go downhill rapidly when given considerable amounts of lactose.

Cheese.—Hosoi found that cottage cheese was well digested, whereas grated Swiss cheese in amounts of 26.4 Gm. for each kilogram of body weight was hardly digested at all. We found that Swiss cheese was well digested when it was given in the form of lumps; the residues then never represented more than 32 per cent of the weight of the original ration. At times the percentage was as low as 14 (chart 2).

Cottage cheese continued to be well digested even when given in amounts as large as 102 Gm. for each kilogram of body weight. We were unable with this substance to produce a break in the efficiency of digestion. The residue came through somewhat faster than did those from Swiss cheese.

Cottage cheese given one day always impaired the digestion of food given the following day. Charts 1 and 3 show examples of such effects. Similar deleterious effects were observed after the giving of lard and of lactose.

Meat.—It has been shown by Cannon⁴ that coarse hard particles of food are slow to leave the stomach. It might well be, then, that the digestion of food such as meat, which needs to be broken up first by pepsin, could be improved by being given in the form of lumps which would be retained for some time in the stomach. One might spare the stomach by giving the meat in the form of hamburger steak, but the greater strain put on digestion in the bowel might prove to be too much for it. Actually, Cohnheim⁵ and later Hosoi found that meat is best digested when given in the form of lumps. We have again found this to be true (chart 2), and it now appears that the dog is following a good instinct when he bolts his food unchewed.

2. Mitchell, Helen S.: Comparative Physiological Values of Five Carbohydrates, Based on Growth and Fecal Analysis, *Am. J. Physiol.* **79**:537 (Feb.) 1927.

3. Evans, H. M., and Burr, G. O.: A New Dietary Deficiency with Highly Purified Diets, *Proc. Soc. Exper. Biol. & Med.* **24**:740, 1927.

4. Cannon, W. B.: *The Mechanical Factors of Digestion*, London, Edward Arnold, 1911, pp. 227.

5. Cohnheim, Otto: *Beobachtungen über Magenverdauung*, München. med. Wchnschr. **2**:2581 (Dec. 24) 1907.

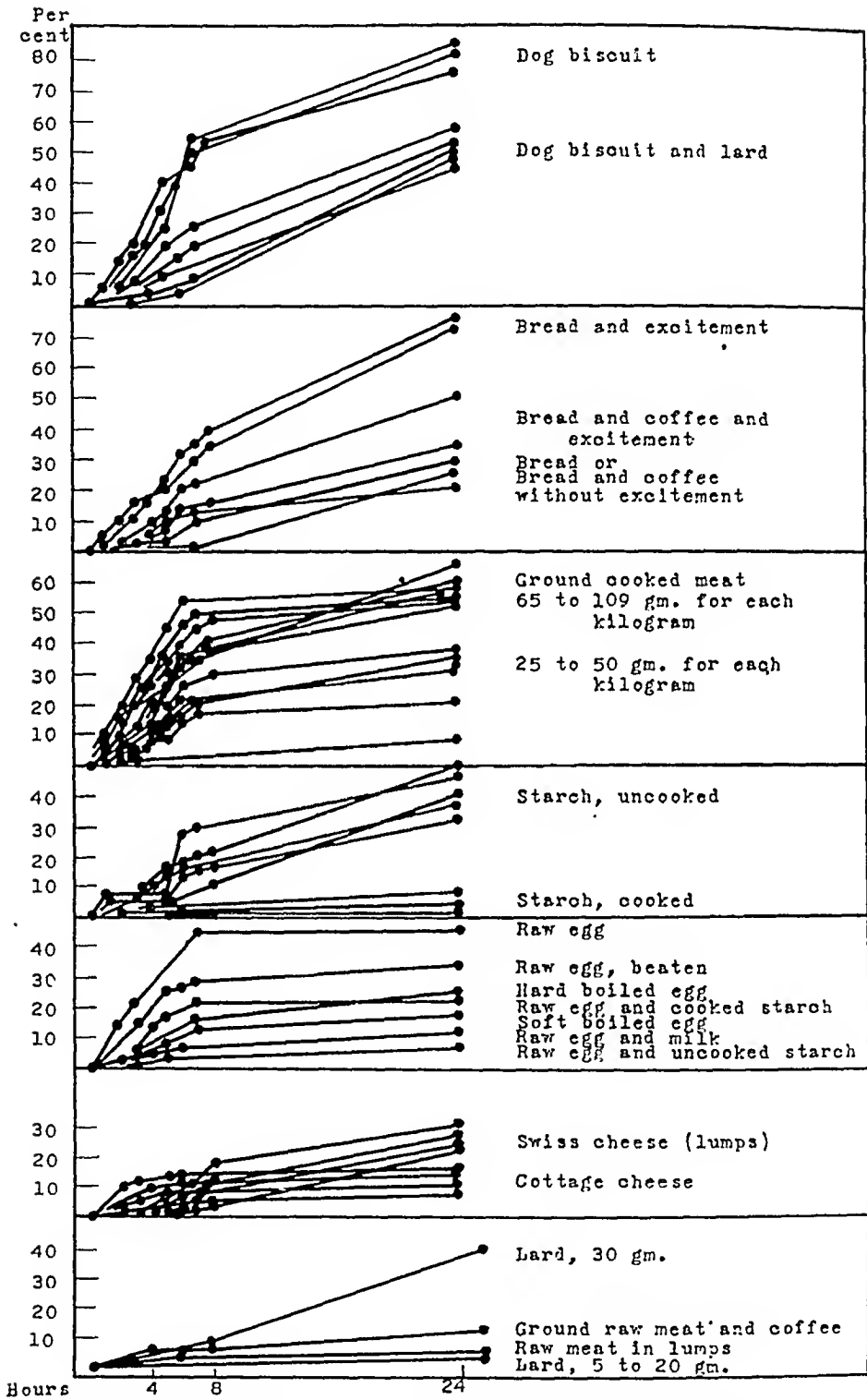


Chart 2.—The effect is shown of adding one food to another, the effect of excitement, the effect of giving large quantities of food, the effect of cooking of food, the difference in the digestibility of two types of cheese and the effect of hashing the food.

Cannon observed, years ago, that the mixing of fat with protein or carbohydrate would cause these two foodstuffs to leave the stomach more slowly than they otherwise would. In the experiments here reported a dog biscuit containing bone-meal, flour and chopped meat was first tested, and it was found to leave a residue of from 80 to 87 per cent. Lard was then mixed with, or melted into, the broken biscuit, and the residue was found to have decreased to about 50 per cent (chart 2). Possibly the fat caused the biscuit to stay long enough in the stomach so that more of it could be attacked by the gastric juice.

Eggs.—Hosoi confirmed what has been known for some time—that raw egg albumin runs through the digestive tract so rapidly that much of it reaches the ileocecal sphincter unchanged. Soft-boiled and hard-boiled eggs were digested much better. Rose and MacLeod⁶ found that raw egg white was better utilized after it was beaten up with air, and this we have confirmed (chart 2). In our experiments, raw whole egg left a residue of from 35 to 60 per cent. Soft-boiled eggs left the smallest residue. Raw egg produced foul, foamy, liquid discharges in which the egg albumin was so little altered that the dogs sometimes ate it again.

The addition to raw egg of raw starch which is not digested by the dog, and which greatly slows the progress of material through the intestine appeared to improve the digestion of the egg. Whereas, the residue from raw egg amounted to from 25 to 36 per cent and that from raw starch amounted to 45 per cent, the residue from both together was usually between 17 and 25 per cent, and on one occasion it was only 7 per cent.

The addition of milk to raw egg resulted in a mixture which was better digested than milk alone. The popular use of egg-nog, without alcohol, would therefore appear to be well justified.

Bread.—Hosoi found that the residue from white bread amounted to from 44 to 52 per cent. In our experiments the results were considerably better, and the percentage varied between 26 and 41 (chart 3). As was to be expected, graham bread left considerably larger residues than did white bread. Strange to say, these residues were decreased in amount when milk or coffee was given with the bread. This improvement in digestion was more marked with sour milk than with sweet milk.

Starch.—Raw cornstarch given in a 33 per cent watery suspension gave fecal residues varying between 36 and 50 per cent (chart 2). Our impression was that practically none of this starch was digested because both macroscopically and microscopically the material recovered appeared

6. Rose, Mary S., and MacLeod, Grace: Some Human Digestion Experiments with Raw White of Egg, *J. Biol. Chem.* 50:83 (Jan.) 1922.

to be unchanged. Strange to say, it passed through the digestive tract slowly, requiring more than twenty-four hours. It probably was caught here and there in the valvulae conniventes.

Dextrose.—As Hosoi showed, dextrose and sucrose are completely or almost completely absorbed. The efficiency of digestion depends somewhat on the concentration of the material given. In one of our experiments in which a concentrated solution of dextrose was administered, it produced such severe vomiting that a lump of formed feces was finally brought up. In only about half of the experiments could the dogs retain a 50 per cent solution of dextrose given in amounts representing about 40 cc. for each kilogram of body weight. When they did retain it, all the sugar was apparently absorbed, because the residues were about the size of those that one would get from a fasting bowel. Strange to say, chocolate candy with cream centers left a residue of from 25 to 50 per cent.

The mixture of Karo syrup and milk which is used in the laboratory for the feeding of animals after operation was well utilized. From 17 to 27 per cent appeared in the feces, as compared with from 35 to 50 per cent for milk alone.

Potatoes, Stewed Tomatoes, Baked Bananas, Stewed Prunes, Stewed Corn and Beets.—These foods were all poorly digested and gave residues varying in amount from 30 to 75 per cent. Digestion could be improved somewhat by the addition of gravy or milk to the foods. Potatoes were better digested when given in lumps than when given mashed.

Baked bananas left a residue which was remarkably constant in its amount, about 37 per cent. Our observations, therefore, do not support the statements of those investigators who have made the claim that cooked banana is a highly digestible food. In Hosoi's experience raw banana was the most poorly digested of all the foods studied.

Rice appeared to be almost perfectly digested. Peptone was also well digested and absorbed.

Fruit Juices.—The dogs were given mixtures of equal parts of orange juice or lemon juice and water, either alone or with meat. The addition of a little meat caused the dogs to drink the liquid voluntarily. The orange juice gave a residue of from 11 to 13 per cent. When added to meat, the amount of residue usually obtained with this food was not increased. The giving of lemon juice resulted in an excretion of residues amounting to from 20 to 55 per cent. It is probable that acids increase the rate of passage of material through the bowel, and this would account for the poorer digestion observed with lemon juice.

Coffee.—Coffee when given with bread or meat appeared to be as well absorbed as water (chart 3). The stools tended, however, to become loose.

Desserts.—Miller, Fowler, Bergeim, Rehfuß and Hawk,⁷ who studied the rate of emptying of the stomach in normal students, concluded that, so far as gastric digestion is concerned, pies with crusts are not particularly harmful. Pudding left the stomach a little faster than pie, and pie left faster than cake. In one dog in which complete colectomy had been performed, custard pie gave a residue of 28 per cent; cornstarch pie, 36 per cent; pie crust, 48 per cent; apple pie, 55 per cent and prune pie, 74 per cent.

INFLUENCE OF VARIOUS FACTORS ON DIGESTION

Forced Feeding.—There have been a number of observations in the past which have led experimenters to believe that food eaten freely with appetite will leave the stomach more rapidly than food given by stomach tube. We, however, have been unable to detect any difference in the amount of fecal residue obtained when foods were given in these two ways.

Anxiety and Excitement.—As has been pointed out in a recent review by Alvarez,⁸ anxiety and excitement tend to retard digestion, and evidences of this were noticed during the progress of the studies reported here. One of the dogs, a nervous, restless animal, fretted a good deal when restrained in the type of sling in which his fellows dozed. Under these circumstances, the fecal residue from bread and butter was about 77 per cent of the amount ingested. Later when he lay quietly in a metabolism cage, the percentage dropped to 41 per cent (chart 2). The other dog with a fistula, that was quiet and well behaved, digested just as well when in the sling as when in a cage.

Heat and Cold.—It has been thought by some writers that the temperature of the food might influence the completeness of digestion, but Hawk⁹ and his associates could not detect any such effect and neither could we.

Several Small Feedings as Compared With One Large Feeding.—Hosoi, Alvarez, and Mann suggested that better absorption of foodstuffs might be secured if small amounts were given at short intervals, and

7. Miller, R. J.; Fowler, H. L.; Bergeim, Olaf; Rehfuß, M. E., and Hawk, P. B.: The Gastric Response to Foods. XII. The Response of the Normal Human Stomach to Pies, Cakes and Puddings, *Am. J. Physiol.* **52**:248 (June) 1920.

8. Alvarez, W. C.: Ways in Which Emotion Can Affect the Digestive Tract, *J. A. M. A.* **92**:1231 (April 13) 1929.

9. Miller, R. J.; Bergeim, Olaf; Rehfuß, M. E., and Hawk, P. B.: Gastric Response to Foods. XI. The Influence of Tea, Coffee and Cocoa upon Digestion, *Am. J. Physiol.* **52**:28 (May) 1920.

Barium Sulphate.—Alvarez and Freedlander¹¹ suggested that the addition of a large amount of indigestible material such as barium sulphate to a meal might act as a laxative and might increase the rate of progress of material through the digestive tube. Some of the dogs were given condensed milk with varying amounts of barium sulphate and acacia. Under these conditions, the excretion of residues from milk was found to be more rapid and the amounts obtained were larger.

Morphine.—Plant and Miller,¹² who studied the effect of morphine on dogs with a Thiry-Vella fistula, found that it increased the tonus and peristaltic activity of the bowel and lessened the tonus of the gastric musculature. They concluded that the giving of morphine resulted in more complete digestion, because the food stayed a longer time in the stomach.

In the experiments reported here the dogs were given canned ground horse-meat and thirty minutes later were given, hypodermically, from 0.03 to 0.06 Gm. of morphine sulphate. Vomiting often occurred, and the animals remained somnolent for about eight hours. During this time practically no residue appeared. During the night, residue amounting to about 20 per cent was passed, and during the following day more was obtained (chart 3). In some of the animals an increase in intestinal tonus immediately after the giving of morphine showed itself in a sudden spurting of intestinal contents from the ileal fistula.

Reaction of the Intestinal Contents.—The residue was usually alkaline to litmus, but with some foods it was acid. It was often acid after the giving of lard, milk and lard, milk and potato, milk and raw egg and sour milk and bread.

COMMENT

It has long been claimed by certain food faddists that in prescribing for the sick the essential point is to secure right combinations of food and to avoid wrong ones. It sounds reasonable, but we have not been able to find much convincing scientific evidence which would favor the theory or help the inquirer in the search for good combinations. The experiments here reported now show that the addition of certain foods to others does help or hinder their digestion, and the way is opened for the study of what may prove to be an important branch of dietetics. It is remarkable to see how the residues from two foods eaten together may be smaller than those of either food eaten separately, and it is

11. Alvarez, W. C., and Freedlander, B. L.: Rate of Progress of Food Residues Through the Bowel, J. A. M. A. **83**:576 (Aug. 23) 1924.

12. Plant, O. H., and Miller, G. H.: Effects of Morphine and Some Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal. I. Action of the Small Intestine in Unanesthetized Dogs and Man, J. Pharmacol. & Exper. Therap. **27**:361 (June) 1926.

even more surprising to see that two almost completely indigestible substances such as raw egg and raw starch are well handled when given together.

Food eaten on the day following the ingestion of certain substances will be imperfectly digested. Alvarez has noted for years that persons just recovering from an attack of diarrhea often have so little ability to digest anything that for a few days they must partake sparingly of only the more digestible foods. When such a person begins immediately to eat everything, he sometimes suffers for months with indigestion, because the irritating residues from one poorly absorbed meal make it impossible for the subsequent meals to be digested properly.

The fact that purgation interferes with digestion and absorption must also be kept in mind when the physician is trying to help patients complaining of flatulence, abdominal discomfort and undernutrition. He cannot tell how much of the disturbance is due to purgation and how much to organic disease until he frees the bowel from insult not only by chemical irritants but also by the now commonly used mechanical irritants such as bran. Often great relief from symptoms can be obtained if the lower bowel is emptied, when necessary, by enemas of warm physiologic solution of sodium chloride.

These experiments suggest that certain patients may be injured if their food, during the process of preparation in the kitchen, is too finely chopped. Our observations also offer some explanation for the occasional deleterious effects of eating between meals. They also suggest that lactose should be given with care, and that its effects should be watched because it can do much harm.

SUMMARY

The amount of residue obtained after the digestion of various foods has been studied in six dogs, all deprived of the colon. The foods best digested were meat, rice, dextrose and fat in small amounts. These foods might well be used in the treatment of patients with diarrhea, and in the preoperative or postoperative care of patients with serious diseases of the colon, rectum or anus.

The combining of certain foods such as bread and milk and raw egg and milk, improved the digestion of both substances. Lactose, when given in considerable amounts, proved to be a laxative which interfered not only with the digestion of food eaten the same day but also with the digestion of food eaten the following day. Cheese and lard given one day also interfered with the digestion of food eaten the following day.

Meat was better digested when given in lumps than when given finely comminuted. The same was true of Swiss cheese. Raw meat was better digested than cooked meat.

Except in the case of a few foods, it was difficult to give enough so that the efficiency of digestion would fail. The dog usually protected himself by vomiting part of the meal.

Raw egg when not mixed with other foods was highly indigestible. Raw cornstarch given alone was almost completely indigestible.

The addition of lemon juice to food hurried the progress of residue through the bowel and interfered somewhat with the efficiency of digestion. Orange juice had little effect on digestion.

Pie crust did not seem to be much more indigestible than white bread. It was more digestible than graham bread.

Anxiety and excitement influenced adversely the efficiency of digestion.

Food when taken in one large amount was better utilized than when taken in several fractions at half-hourly intervals. Apparently each feeding stimulated peristalsis and caused the food to pass too rapidly through the bowel. Purgatives, sodium bicarbonate and barium sulphate interfered with digestion. Morphine slowed the progress of material through the bowel. It had little effect on the digestion of ground cooked meat, given at the same time, but it interfered with the digestion of meat given the next day.

ADDISON'S DISEASE IN A NEGRO

REPORT OF A CASE *

ANGELO M. SALA, M.D.

AND

MENDEL JACOBI, M.D.

NEW YORK

Addison's disease, contrary to the opinion of Addison himself, who felt that its recognition would show it of rather frequent occurrence, is relatively infrequent. Among white people in whom pigmentary changes lead to a diagnosis or suspicion of the disease with some ease, estimations of the frequency vary. Osler¹ stated that he saw only seventeen cases in the United States in twenty-one years. In 1925, Rowntree² was able to collect forty-seven cases (16 per hundred thousand cases registered) from the Mayo Clinic records of the preceding thirteen years.

Because of the difficulties of recognizing the disease in Negroes attendant on their color, the diagnosis of Addison's disease is apparently rarely suspected and still more infrequently made and confirmed. In a careful search of the literature for the last forty years, we have been able to find but four recorded cases, only two of which came to autopsy. We record a case occurring at the Harlem Hospital, where the greater portion of the patients are colored.

CASE REPORT

D. R., a colored man, aged 51, was admitted to the Harlem Hospital on July 10, 1927. No definite or detailed history was obtainable, except that he had been ill for about two months, rapidly losing weight and becoming very tired and weak. No pulmonary symptoms were present. He had been totally bedridden for the last two weeks; he had begun then to experience great difficulty in speaking, was exceedingly hoarse, and had some pain in his throat.

Physical examination revealed an acutely ill colored man, about 50 years of age. He was markedly emaciated. The respiration was shallow but equal on both sides; the breath sounds and vocal fremitus were diminished throughout; the percussion note was somewhat dulled generally with areas of high-pitched resonance scattered throughout the chest, and occasional moist râles were present. The heart sounds

* Submitted for publication, Dec. 10, 1929.

* From the Pathologic Laboratories, Harlem Hospital, and Brownsville and East New York Hospital, Brooklyn.

1. Osler, quoted by Dock and Lisser, in Osler, William, and McCrae, Thomas: *Modern Medicine*, ed. 3, Philadelphia, Lea & Febiger, 1926, vol. 5, p. 273.

2. Rowntree, L. G.: *Studies in Addison's Disease*, J. A. M. A. **84**:327 (Jan. 31) 1925.

were of poor quality, regular but distant; no murmurs were heard. The abdomen was scaphoid, the wall thin and emaciated; there were no palpable masses. The temperature on admission was 100 F.; the pulse rate, 110, and the respiratory rate, 40. Attempts at making blood pressure readings were unsuccessful. Stimulative treatment was immediately instituted, but there was no response, and the patient died twelve hours after admission. The antemortem diagnosis was probable malignancy with cachexia.

Autopsy was performed sixteen hours after death. The body was that of a poorly developed, markedly emaciated colored man, with loose skin that was boggy over the chest wall. The fingers were markedly clubbed. The abdomen was scaphoid. There was a large, oval, cystic bulge present in Scarpa's triangle on the right side. No pigmentation of the mucous membranes of the mouth or lips, or of the nail-beds was apparent. The larynx showed a dry, pale, smooth mucosa, without ulceration; no tubercles were present. In the right lobe of the thyroid there was a cystic adenoma. Above the pulmonary apex on the right, at the root of the neck, a firm, movable, deeply blackened anthracotic lymph node was present.

The interlobular fissures of both lungs were obliterated by firm, fibrous adhesions. The right and left upper lobes were firmly adherent to the lateral and posterior walls of the chest, and the pleural cavities were obliterated; the visceral pleura covering the lower lobes was dulled but not covered by exudate. In the right upper lobe, extending anteriorly from the extreme apex to the third rib there was a large, multiloculated cavity lined by a thin, shaggy, green, fibrino-purulent membrane. The loculi communicated with one another and with the eparterial bronchus. They were filled with thick, odorless, creamy material. The cavity was surrounded laterally and above by a thin strip of firm, airless, grayish-red lung tissue. Throughout the remainder of the right upper and lower lobes were numerous discrete and confluent, firm, grayish-white areas, sharply demarcated; in the right middle and left upper lobes such areas were rather more infrequent, while very few were present in the left lower lobe. The intervening lung tissue was crepitant. At the hilus, more particularly on the right side, were several discrete, large, firm anthracotic lymph nodes.

The heart weighed 200 Gm. The pericardium was thick and opaque. Little epicardial fat was present; the heart muscle (particularly the papillary muscle) was pale and diffusely permeated with yellow streaks. The coronary arteries, the aorta and the abdominal branches of the latter contained numerous subintimal, atheromatous and calcific plaques.

In the thickened omentum and the parietal peritoneum were numerous discrete, round, sharply demarcated nodules (about 3 mm. in diameter), firm and gritty, which cut with difficulty. A few old fibrous strands were present between the ileal and the jejunal coils. The liver weighed 1,200 Gm.; its surface was smooth and its lobular structure quite distinct on section. The spleen weighed 120 Gm.; its capsule was wrinkled and thickened; the corpuscles were distinct on the cut surface, and there were no tubercles. The kidneys weighed 235 Gm. each; bilateral double ureters were present, the two ureters opening into the same major calix on the right, into separate calices on the left, and into the bladder by four distinct openings. No other gross changes were present in the kidneys or bladder, nor in the gallbladder, bile ducts or pancreas.

The right suprarenal gland weighed 9 Gm.; it showed no gross morphologic changes. The left weighed 23.4 Gm. It covered the entire upper pole of the kidney, extending mesially caudad to overlap the renal hilus. It was roughly shaped like a bean; its capsule was everywhere intact, and it was easily separable from the kidney and the surrounding tissue. The entire gland was firm, almost

hard in consistency. On section, no cortex or medulla was apparent. Instead, several large, homogeneous, firm, irregularly outlined nodules of structureless, yellow, opaque tissue filled the entire organ, the largest measuring 3 by 1 cm. and occupying the entire upper half. Between these nodules were narrow, pale, dull brown strands of tissue resembling medullary tissue. No softened areas were present.

The right testis and epididymis were not grossly altered. No testis could be found on the left side either in the scrotum or in the widened inguinal canal or intra-abdominally. The left spermatic cord was a firm, grossly structureless mass of fibrous tissue.

The dorsal part of the spine was scoliotic to the left; the fifth, sixth and seventh vertebrae were wedge-shaped and collapsed anteriorly. The anterior and right lateral surfaces of the sacrum were roughened and eroded. Large, soft, caseous lymph glands covered its surface. In the right psoas muscle, from the level of the second lumbar vertebra downward into Scarpa's triangle, there was a large multiloculated cavity lined by a thick, shaggy, greenish necrotic membrane and filled with about a pint of odorless, greenish white pus. This cavity communicated with a smaller similar one lying in the tissues adjacent to the terminal sacrum and coccyx. The lumbar vertebral bodies or processes were not involved. The mesenteric lymph nodes showed no gross changes.

A smear from the cavity in the psoas showed acid-fast bacilli and gram-negative short bacilli, much fibrin, many lymphocytes and degenerated polymorphonuclear leukocytes.

Microscopically, the lungs (through the abscess wall) showed confluent caseous areas containing and surrounded by multinucleated giant cells. The adjacent alveolar walls were hyalinized and had no demonstrable capillaries; a few alveoli were filled with granular fibrin, varying numbers of lymphocytes and a few large endothelial cells, usually uninucleated, but grouped together and with indistinct cell borders. Sections through other portions of the lungs showed numerous minute tubercles composed of endothelial cells and central multinucleated giant cells in the alveolar walls, and often filling the alveolus. No septal or vascular fibrosis was apparent.

The right suprarenal gland showed only a paucity of fat vacuoles in the cortex; the left (region of the large mass in the upper half) showed a wide capsular zone of coarse, dense connective tissue diffusely infiltrated with lymphocytes. Immediately beneath this layer were a few small columnar cells containing a small amount of clear, homogeneous acidophilic cytoplasm and a small, deeply basophilic nucleus. These cells were arranged in coiled masses or short fascicular strands between a fine fibrous network. The remainder of the tissue consisted of caseous matter containing a few multinucleated giant cells. Strands of the subcapsular cells, poorly stained and often without nuclei, were present between the caseous masses. Sections through the lower portion of the suprarenal showed numerous tubercles, with caseous centers, lying in the cortex and medulla, the cells of both of which were compressed.

The liver showed marked fatty vacuolation of the cord cells. Here and there an occasional multinucleated giant cell surrounded by a few lymphocytes and necrotic liver cells was found in the parenchyma. No relation between these areas and the portal space or central vein was apparent.

The spleen showed numerous small necrotic areas irregularly scattered within the pulp. These areas showed no giant cells; in places, a few faintly outlined, elongated cells resembling epithelioid cells were seen.

Sections of the peritoneal nodules showed them to consist of calcific, granular material surrounded by fibrous tissue heavily infiltrated with lymphocytes. Sections of the abdominal lymph nodes showed no changes; those along the sacrum showed numerous caseous areas surrounded by multinucleated giant cells. Sections through the psoas abscess wall showed tuberculous granulation tissue. No tubercle formation or caseation was apparent.

COMMENT

The case reported is obviously one of long-standing pulmonary and bony tuberculosis, terminating rapidly after involvement of the non-cavitated pulmonary lobes and the suprarenal in a manner suggestive of blood stream invasion. The presence of the calcific nodules in the peritoneum is suggestive of an earlier, healed, peritoneal tuberculosis; their discrete arrangement even suggests a miliary distribution.

Of importance is the rapid course of the disease in its acute suprarenal involvement and the total absence of increased pigmentation.³ In the other cases recorded in Negroes, pigmentary changes, especially darkening of the palms and soles, was a striking feature. None, however, was of such short clinical duration as our case. Of the two cases that went to autopsy, one showed cavitation of the suprarenal gland, the other extensive hyalinization and fibrosis, both indicative of a rather long-standing process. Of the recorded cases in Negroes, Lemann's⁴ patient noted a darkening and discoloration of his forearms and face progressing over his entire body one year before death occurred. Lemann described his patient as of "stove-polish" or "shoe-black" color, especially the hands, face, forearms, feet and lower part of the legs, saying that "he was the blackest Negro seen in the clinic." Biopsy of the skin showed marked pigmentation of the chromatophores.

Two of Evans' ⁵ patients showed an increase of body pigmentation for more than one year; the third noted brown discolorations on the dorsa of her hands and feet for a year, and showed a slight increase in pigmentation over the borders of the tongue at the junction of the anterior and middle thirds. Of the two patients examined post mortem, Evans' showed scattered areas of black and dark brown pigmentation on the buccal mucosa, the hard and soft palate, and under the tongue, while Lemann's patient showed dark discolorations of the gums and dark spots on the tongue and buccal mucosa.

Our case presented symptoms for but two months. In the two cases just quoted, one patient ⁴ died one and one-half years after the onset

3. Chvostek, quoted by Hektoen: *American Text-Book of Pathology*, Philadelphia, W. B. Saunders Company, 1902, p. 923.

4. Lemann, I. I.: *Addison's Disease: Report of Three Cases, Including One in a Negro*, *New Orleans M. & S. J.* **78**:814 (June) 1926.

5. Evans, L. S.: *Addison's Disease in the Negro: Report of Three Cases*, *Am. J. M. Sc.* **176**:499 (Oct.) 1928.

of symptoms, the other,⁵ five years after coming under observation and two years after the diagnosis was made. The other two patients whose cases were reported⁵ were alive and in fair condition one year after the onset of the symptoms. The consensus of most authors is that an acute course is rare in white patients.⁶

Weakness as the presenting symptom was present in all cases. Gastro-intestinal symptoms occurred in four patients; vomiting was present in two,⁵ usually without relation to meals and most often in the morning; diarrhea occurred in all four.⁷ In all reported cases, as well as in our own, marked anorexia appeared early in the symptomatology.

Of considerable prominence in this group of cases are symptoms referable to the respiratory system and larynx. Our patient complained of soreness when talking; he was quite hoarse when seen in the hospital. One of Evans' patients had been so hoarse that she "could not talk above a whisper" for a month; no pain on talking is noted. Choking sensations were periodically present, accompanied by dizziness and a feeling of faintness in the case that came to autopsy. No note is made of any lesions of the larynx or respiratory tract other than the presence of two small tubercles in the right lung and an adherent pleura bilaterally. Our case likewise showed no lesions of the larynx; the pulmonary pathologic process does not appear to be sufficient to explain the pain and hoarseness. We feel that these symptoms are probably the expression of the general asthenia; the soreness noted was perhaps the result of repeated forcible attempts to speak loudly, with a consequent local laryngeal irritation.

In three of the cases recorded there was a past history suggesting tuberculosis: one of Evans' ⁵ patients had an abscess of the chest wall which was opened three years before the onset of pigmentary changes; another had a fistula in ano for several years, and a third had pneumonia associated with a pleurisy for one month ten years before observation. In the other case⁴ there was a history of syphilis and gonorrhea. There was no history of familial tuberculosis present in any case.

Among white people, the disease is most frequent in males (Kaufmann, Timme⁶). In the short series of the disease in Negroes, three cases occurred in female and two in male patients. Whereas most of the cases in white persons occur between the twentieth and fortieth years, none of the Negroes was under 30; one was 36, and two were 51.

6. Osler (footnote 1). Kaufmann: *Spezielle pathologische Anatomie*, ed. 8, Berlin & Leipzig, Walter de Gruyter & Company, 1922, vol. 11, p. 1004. Timme, W., in Cecil: *Text-Book of Medicine*, Philadelphia, W. B. Saunders Company, 1927, p. 1133.

7. Lemann (footnote 4). Evans (footnote 5).

Two of the previously recorded cases came to autopsy. Lemann's case showed in the suprarenal glands irregularly lobulated masses 8 by 2 cm., pale yellow and surrounded by fat. The cut surface of each was studded with numerous yellow areas of various size, some of the larger areas showing central necrosis, cavitation and calcification. Microscopically, these areas were typical tubercles. The lungs contained numerous tubercles of various sizes and a small cavity at the right apex. A few recent tubercles were present in the kidneys and retroperitoneal lymph glands. The case was apparently one of tuberculosis of the lungs and suprarenal gland of some duration, ending in a terminal miliary dissemination. Syphilitic aortitis was an associated condition.

In Evans' case, the left suprarenal was small, flat, firm and more nodular than the right. It was peculiarly hard on section; no cortex or medulla was distinguishable, the gross observation of a general fibrosis being made; no caseation was grossly visible. Histologically, the involved suprarenal gland showed extensive hyalinization and fibrosis and typical tubercles without necrosis. The lungs showed extensive pleural adhesions, slight anthracosis and several apical tubercles. The heart was atrophic (98 Gm.). The kidneys were small, flabby and atrophic, with flattened pyramids; there was a small tubercle on the surface of the right kidney. Microscopically, there were patches of cellular infiltration of the cortex near the capsule, with atrophic glomeruli, thickened glomerular capsule and shrunken tubules.

CONCLUSION

Including our own, only five cases of tuberculous involvement of the suprarenal glands in Negroes are on record, a rather surprising fact in view of the frequency of pulmonary and miliary tuberculosis in the race. In this series of cases, females were more frequently affected than males (3:2), as against an average of (2:1) greater frequency in males among white people. The age incidence in these cases was somewhat higher than in white people. Pigmentary changes did occur in the cases of considerable duration. These involved areas usually uninvolved in white people (nail-beds, soles and palms), although this distribution may be due merely to the more ready recognition of pigmentary changes in these areas in colored patients. Changes in general pigmentation may become extreme and extensive. In the acute forms, pigmentary changes may be absent.

The course in the cases recorded was more rapid than in white people. Nervous symptoms were not prominent in any case. Laryngeal symptoms—hoarseness, pain on speaking and a choking sensation—were prominent, or even presenting, symptoms in this group of cases. No local evidence to explain these symptoms was present. Asthenia was

a prominent symptom; anorexia was marked. In all cases, except in those in which pigmentary changes and gastro-intestinal and asthenic symptoms were marked, the diagnosis, always difficult to make in white people, was extremely difficult; in the acute case, it was not often made except at autopsy.

SUMMARY

The fifth case of Addison's disease in a Negro, with autopsy observations, is recorded in detail. The other recorded cases are reviewed.

A comparison is made with the disease in white persons. The difficulty of diagnosis and the prominence of symptoms not usually stressed in white people are emphasized. The laryngeal and respiratory symptoms are stressed particularly.

CHEMISTRY AND METABOLISM IN EXPERIMENTAL YELLOW FEVER IN MACACUS RHESUS MONKEYS

II. NITROGEN METABOLISM *

A. MAURICE WAKEMAN, M.D.

AND

CLARE A. MORRELL, M.A.

NEW HAVEN, CONN.

In the preceding paper,¹ determinations of nonprotein nitrogen and its individual nitrogenous components in the blood of normal *Macacus rhesus* monkeys and similar animals infected with yellow fever were presented. It was shown that in the terminal stage of yellow fever, the amino-acid nitrogen in the blood increased greatly, both in absolute magnitude and in proportion to total nonprotein nitrogen and other individual nitrogenous constituents. Urea nitrogen, on the other hand, did not rise, or rose little in proportion to amino-acid and total nonprotein nitrogen. In a few instances it actually diminished. The nature of the observed changes indicates that the chief disturbance of nitrogenous metabolism in yellow fever is the destruction or impairment of the power of the liver to deaminize amino-acids and to form urea.

However, definite conclusions cannot be drawn from studies of the blood alone. In order to estimate the rates of formation and destruction of nitrogenous metabolites, simultaneous studies of blood nitrogen and total nitrogen metabolism were carried out on a series of monkeys infected with yellow fever. These studies, which are reported in this paper, confirm the results of studies on the blood reported in the preceding article.¹ Uric acid metabolism remains essentially unaltered, but the functions of deaminization and urea formation are profoundly injured.

The technic employed in the metabolism experiments was described in detail in the first paper.¹

Only protocols of typical experiments are given. Those which have been chosen are, however, representative and afford a complete picture of the metabolic disturbances encountered.

* Submitted for publication, Jan. 30, 1930.

1. Wakeman, A. M., and Morrell, Clare, A.: Chemistry and Metabolism in Experimental Yellow Fever in *Macacus Rhesus* Monkeys: I. The Concentration of Nonprotein Nitrogenous Constituents in the Blood, Arch. Int. Med. **46**:290 (Aug.) 1930.

Protocols of the experiments are given in the following paragraphs, and corresponding metabolism data are presented in tables 1 to 5 inclusive.

CHANGES IN THE NONPROTEIN NITROGENOUS CONSTITUENTS OF BLOOD AND URINE DURING THE TERMINAL STAGE OF YELLOW FEVER: EXPERIMENTAL WORK

EXPERIMENT 1.—*Macacus rhesus* M3, a large male in good condition, was fed diet no. 3, beginning on April 28. On April 29, the animal was infected by a mosquito bite. On May 2, it was quite normal in appearance, and a blood sample

TABLE 1.—*Changes in the Nonprotein Nitrogen Constituents of Blood and Urine During the Terminal Stage of Yellow Fever in Monkey M3*

Blood Taken		Non-protein Nitrogen, Mg. per Cent	Urea Nitrogen, Mg. per Cent	Amino-Acid Nitrogen, Mg. per Cent	As per Cent of Total Nitrogen		Sugar Mg. per Cent	Comment
					Urea Nitrogen	Amino-Acid Nitrogen		
May 2, 2 p. m., from right foreleg		43	20	8	46	18	109	Last meal at 9:30 a. m.
May 3, 8:10 a. m., from right foreleg		61	17	15	28	25	66	Last meal at 4:30 p. m. May 2
May 3, 4:10 p. m., from right foreleg		67	15	17	22	25	113	Last meal at 9:10 a. m.
May 3, 10:15 p. m., from heart; 10 minutes post-mortem		99	5	33	5	33	15	Last meal at 5 p.m.

Date	Urine Volume, Ce.	Urine Nitrogen as						As per Cent of Total Nitrogen		Acetone	Temperature	
		Total, Mg.	Urea, Mg.	NH ₃ , Mg.	Urea + NH ₃ , Mg.	Amino-Acid, Mg.	Rest, Mg.	Urea + NH ₃	Amino-Acid		A. M.	P. M.
April 28	37	485	563	47	610	17	358	63	2	Negative	102.0	102.7
April 30	35	445	235	25	260	10	175	58	2	Negative	102.0	102.7
May 1	65	712	407	45	452	18	242	63	3	Negative	102.7	103.5
May 2 *	65	836	504	36	540	23	273	65	3	Negative	104.4	104.9
May 2 *	65	836	504	36	540	23	273	65	3	Negative	104.4	104.9

* Weight = 4.3 Kg.

† Died at 10:05 p. m.

‡ Specimen voided at 3:00 p. m.

was taken. On May 3, it was drowsy but vigorously resisted handling when the second blood sample was taken at 8:10 a. m. It was lying down, weak and listless at 4:10 p. m. when the third blood sample was taken; at 7:10 p. m. it was lying down and was unconscious. Death occurred at 10:05 p. m. A sample of blood was taken from the heart ten minutes post mortem.

The urine had been tested each day for acetone with the possibility in mind that there would be a long premortal period with a low blood sugar level. Such was not the case, and it was not until shortly before death that the blood sugar fell below the normal level.

The results of blood and urine studies are recorded in table 1.

This experiment was chosen for presentation because it illustrates the rapidity with which the blood changes develop during the last hours of the disease. It does not permit exact estimation of nitrogen metab-

olism, because dietary and stool nitrogen were not determined. The most striking feature of the experiment is the absolute diminution of blood urea in the last six hours of life after urine formation had ceased.

Studies were made to investigate more thoroughly the changes occurring in nitrogen metabolism during the terminal period of yellow fever. Protocols of four typical experiments are given here. One of the animals (M 1) recovered, and three (M 5, M 4 and M 2) died.

EXPERIMENT 2.—*Macacus rhesus* M1, a large male, in good condition, was fed diet no. 1 beginning on August 14; metabolism studies were begun on August 18. On September 1, the monkey was inoculated with 0.5 cc. of Asibi strain blood virus; on September 7, it was reinoculated with 1 cc. of the same virus. September 10, the animal appeared ill, and was found lying down, but arose if disturbed; it vomited 60 cc. of substance between 5 and 8 p. m.

On September 11, the animal was weak after the withdrawal of 12 cc. of blood. The usual diet was replaced by 15 Gm. of cane sugar and 0.2 Gm. of salt in 60 cc. of water, given both morning and evening; at 5 p. m., the animal was distinctly weak. The morning of September 12 found it somewhat brighter, but it vomited in the afternoon. When offered 15 Gm. of cane sugar and 0.3 Gm. of salt in 60 cc. of solution at 5 p. m., the monkey drank a small quantity and upset the remainder. On September 13, it was decidedly better, and appeared quite well. On September 15, a small abscess was drained at the site of the incision over the femoral artery, which healed uneventfully. The monkey appeared normal for the remainder of the experiment.¹

The blood used in the first inoculation was taken on the first day of fever from a monkey that had died on the seventh day after inoculation. Three other monkeys were inoculated with 1 cc. of this blood, two of them one day before, one of them one day after the inoculation of M1; all died. The inoculation on September 7 was made with blood of a monkey taken on the first day of fever. This monkey died after a short illness. Subsequent inoculation of M1 with blood from a monkey which later died, taken on the first day of fever, produced no reaction. From a consideration of this evidence, it seems reasonable to assume that the elevation in temperature produced in M1 by the injection of virulent blood represented an attack of yellow fever which rendered the animal subsequently immune.

The reaction of day and night urine to litmus was tested in each twelve hour specimen. In general, the night urine was more acid than the day. Most specimens of urine passed from 8 a. m. to 8 p. m. were slightly alkaline or neutral, while those passed from 8 p. m. to 8 a. m. were neutral or more often acid. From September 10 to 14 both were distinctly acid. The volume of the night specimen was usually greater than the day urine.

No glycosuria was observed from August 27 to September 16.

The foam test for bile was negative throughout the experiment, although from September 11 to 14 the urine was abnormally dark in color.

On September 11, 131 mg. of protein was present in the urine and a trace and a faint trace were present on September 12 and 13, respectively.

The van den Bergh test revealed no bile pigment in the serum except a faint trace in the blood taken on September 11.

The results of metabolism and blood studies are presented in table 2. The figures represent the average values from duplicate analyses. All decimals have been omitted in this and other tables. This explains the apparent constancy of the daily excretion of uric acid and amino-acid nitrogen in some periods. Differences of less than a milligram of nitrogen are insignificant for the purpose of this study, and convenience and clearness justify their omission in the tables. The figures representing the urine nitrogen fractions as percentage of total nitrogen have also been reduced to the nearest whole number, except in the case of uric acid.

The nitrogen balance was calculated by subtracting the urine plus the feces nitrogen from the diet nitrogen. The rest nitrogen is the remainder after subtraction has been made from total nitrogen of the determined nitrogen fractions.

There is little disturbance of blood nonprotein nitrogen metabolism in this, as in other cases in which recovery occurred. Failure to take the full diet, rise of urinary nitrogen and production of a negative balance from September 10 to 12, inclusive, are the only signs of disease evident in the nitrogen metabolism.

EXPERIMENT 3.—*Macacus rhesus* M5, a large female, in good condition, was fed diet no. 2, beginning on September 2; the metabolism studies were begun on September 13.

On September 22, the blood sample was taken and the monkey was inoculated with 1 cc. of Asibi strain blood virus. It vomited 8 cc. of the diet at 2 p. m. but showed no other signs of illness. On September 25, the monkey vomited 5 cc. of its diet between 2:30 and 4:30 p. m., but it looked well.

On September 26, the animal vomited a small amount of its food at 7 p. m., and on September 27, it was definitely less active; it vomited 5 cc. of the diet at 10:30 a. m. and 5 cc. at 8 p. m. On September 28, a blood sample was taken. The monkey was bright and active in the morning, but lay down in the afternoon. On September 29, it was weaker, lying down when undisturbed. At 11:30 p. m. it was very weak. Death occurred the following day at 6:15 a. m.

At 6:30 a. m., 25 cc. of blood was removed from the heart. When the body was removed from the cage at 6:30 a. m., about 60 cc. of black fluid poured from the nose and mouth. Analysis of this material showed it to contain 198 mg. of nitrogen and 650 mg. of chloride. Five cubic centimeters of dark-colored urine was taken from the bladder, which was then washed with distilled water.

In this experiment the day and night urine was analyzed separately, on the supposition that during an attack of yellow fever, alterations might be more easily demonstrated in the shorter periods. However, this was not found to be the case and only the results of twenty-four hour periods are presented in table 3. The small day volume compared with the night volume was attended by the excretion of larger amounts of nitrogen during the night.

The nonprotein nitrogen in the serum on September 28 was found to be 28.6 mg. per cent of the serum. Since this value was within the

TABLE 2.—Nitrogen Metabolism During Yellow Fever in Monkey M1

Date	Weight, Kg.	Urine Volume, Cc.	Total Nitrogen			Urine Nitrogen as					Organic Acid, Tenth Normal	Phos- phorus, Mg. per Cent	Serum Nonprotein Nitrogen, Mg. per Cent	Tempera- ture, F.	
			Urine, Mg.	Stool, Mg.	Balance, Mg.	Urea, Mg.	NH ₃ , Mg.	Urea + NH ₃ , Mg.	Amino- Acid, Mg.	Inine, Mg.	Uric Acid, Mg.	Rest, Mg.			
August 28.....	2.88	38	810	454	243	385	16	401	6	35	1	11	52	66
August 29.....		45	810	583	117	416	21	437	8	39	2	73	55	9
August 30.....		48	810	576	110	432	23	455	7	39	2	73	51	11
August 31.....		48	810	709	—9	477	28	505	6	38	2	158	51	18
Average.....		45	810	581	119	423	22	449	7	38	2	85	52	12	
Per cent of total nitrogen		73	4	77	1	6	0.3	14			
September 1*.....	2.88	33	810	275	465	146	23	170	4	27	1	73	28	12	103.2
September 2.....		41	820	419	321	286	27	313	10	40	2	51	50	5	101.2
September 3.....		52	810	525	70	409	28	437	10	39	2	37	58	6	102.7
September 4.....		43	810	543	70	404	26	430	8	38	2	65	50	13	102.4
September 5.....		50	810	667	73	493	25	515	10	43	2	97	60	9	100.9
Average.....		48	810	538	22	397	26	421	9	40	2	63	51	8	101.9
Per cent of total nitrogen		71	5	79	2	7	0.1	12			
September 6.....	2.96	42	805	635	127	492	26	518	9	41	2	62	55	14	102.1
September 7.....		41	820	645	132	383	17	400	8	46	2	190	62	28	103.2
September 8.....		41	835	593	199	378	20	398	8	43	2	142	50	15	103.1
September 9.....		51	850	737	70	419	21	440	9	47	2	239	54	11	103.4
Average.....		44	827	665	132	418	21	439	9	45	2	158	55	17	102.7
Per cent of total nitrogen		63	3	66	1	7	0.3	21			
September 10.....	2.95	—†	430	1,041	—654	575	30	605	21	45	4	366	104.2
September 11.....		71	...	1,018	—1,010	621	103	727	20	51	6	190	65	25	104.6
September 12.....		—†	430	873	—486	412	82	494	11	48	3	317	102.8
September 13.....		34	820	530	232	279	53	337	9	41	3	110	52	12	100.9
Average.....		52	563	800	—487	472	68	540	15	47	4	253	73	39	
Per cent of total nitrogen		55	8	63	2	5	0.4	29			
September 14.....		29	793	495	231	274	33	307	8	39	3	138	49	21	102.8
September 15*.....	2.81	34	793	335	391	28	101.4
September 16.....		56	793	403	324	231	27	258	10	38	2	95	37	6	101.9
September 17.....		102.3
Average.....		42	793	449	277	252	30	282	9	38	2	116	43	14	...
Per cent of total nitrogen		56	7	63	2	8	0.1	26			

* Some urine lost. Figures not included in average.

† Urine contaminated with vomit. Volume not measured.

normal range, normal values for the nitrogenous constituents of whole blood were assumed. Blood taken from the heart fifteen minutes post mortem contained 65.8 mg. per cent of nonprotein nitrogen; 18.2 mg. per cent of urea nitrogen; 14.5 mg. per cent of amino-acid nitrogen; 0.9 mg. per cent of uric acid, 2.3 mg. per cent of creatinine and only a trace of ammonia nitrogen.

The metabolism data from this experiment are given in table 3.

EXPERIMENT 4.—*Macacus rhesus* M4, a medium-sized male, in rather poor condition, with thin hair and puffy eyelids, feebly resisted handling and was seen to be lying down occasionally. Diet no. 3 was begun on October 22 and the metabolism studies on October 27. On October 31 and November 1, an unknown amount of urine was lost. On November 2, an inoculation with 0.5 cc. of Asibi strain blood virus was given. On November 5, the monkey was lying down and was unconscious; a slight diarrhea was observed. The animal died at 11:15 p. m.

Blood was obtained from the heart ten minutes post mortem. About 8 cc. of urine was recovered from the bladder. Autopsy revealed a well advanced case of yellow fever. No other abnormalities were discovered to explain why the monkey had been in such poor general condition.

This monkey presented a consistently negative nitrogen balance, which increased during the febrile period. The slight diarrhea observed on the last day of life greatly increased the stool nitrogen for this period.

The results of metabolism and blood studies are presented in table 4.

EXPERIMENT 5.—*Macacus rhesus* M2, a large male, was in excellent condition. It was fed diet no. 3, beginning November 8, and the metabolism studies were begun November 15.

On November 19, an inoculation with 1 cc. Asibi strain blood virus was given. The animal vomited 5 cc. of the diet at 8:30 a. m., but showed no other signs of illness. On November 22, it appeared weak and did not resist handling as it usually had. At 4 p. m. it vomited 15 cc. of the diet. On November 23 it vomited and again on November 24, when no feces were passed. On November 25 the monkey was much weaker; no feces were passed. On November 26, weakness increased, and by evening the animal was prostrated. No feces were passed on this day. On November 27, there were large diarrheal stools at 8 a. m. The monkey was unconscious at this time, and died at 10:15 a. m.

The results of metabolism and blood studies are presented in table 5. That stool nitrogen is low in period 2 and high in period 3 is probably referable to the constipation and diarrhea, respectively, which occurred in these periods. The urine on November 22 was light green. On November 26, 312 mg. of protein was found in the urine. There was a striking diuresis during the last day of life that persisted until six hours before death. At 2 a. m. on November 27, 30 cc. of urine was passed, and at 4 a. m., 29 cc. At autopsy, about 0.5 cc. was found in the bladder, and about 150 cc. of black fluid was recovered from the stomach. Since this was greater in volume than the food given on the preceding day, it has been assumed that no food was absorbed on November 26.

The results of the experiment are given in table 5.

TABLE 3.—Nitrogen Metabolism During Yellow Fever in Monkey M5

Date	Weight, Kg.	Urine Volume, Cc.	Total Nitrogen			Urine Nitrogen as				Organic Acid, Cc. Tenths Normal	Phosphorus, Mg.	Serum Nonprotein Nitrogen, Mg. per Cent	Temperature, F.	
			Diet, Mg.	Urine, Mg.	Stool, Mg.	Balance, Mg.	Urea, Mg.	NH ₃ , Mg.	Urea + NH ₃ , Mg.	Amino Acid, Mg.	Creatinine, Mg.	Uric Acid, Mg.	A. M.	P. M.
September 18.....	2.43	41	467	207	60	200	105	22	127	7	25	1	47	103.6
September 19.....		51	467	275	60	132	125	26	151	12	27	1	84	102.6
September 20.....		54	467	233	60	171	117	21	138	7	26	1	61	102.8
September 21*.....		45	467	201	60	203	106	19	125	..	25	103.1
Average.....		48	467	238	60	169	116	23	139	9	26	1	64	103.6
Per cent of total nitrogen		49	10	59	4	11	0.4	27	
September 22*.....	2.52	..	467	...	26	102.4
September 23.....		26	467	145	26	206	54	19	73	4	26	1	41	103.0
September 24.....		19	417	316	26	75	208	21	220	9	23	1	82	103.7
September 25.....		66	387	478	26	117	316	14	330	6	30	1	111	104.0
September 26*.....		19	417	364	26	57	...	23	...	7	29	1	...	104.6
September 27.....		..	387	461	26	100	267	40	307	10	31	2	111	103.6
Average.....		47	417	357	26	77	211	23	234	1	27	1	86	
Per cent of total nitrogen		59	6	65	2	7	0.3	24	
September 28.....	2.47	60	429	372	53	4	187	79	266	13	33	4	62	104.9
September 29 †.....		53	223	237	53	67	116	54	170	5	21	4	37	106.2
Average.....		56	325	304	53	31	151	66	217	9	27	4	49	
Per cent of total nitrogen		50	22	72	3	9	1	16	

* Figures not included in average.

† Died at 6:15 a. m., September 30.

TABLE 4.—Nitrogen Metabolism in Yellow Fever in Monkey M4

Date	Urine Vol. Weight, unce, Kg. Cc.	Total Nitrogen			Urine Nitrogen as			Blood Nitrogen as			Temperature							
		Diet, Mg.	Urine, Mg.	Stool, Balance, Mg.	Urea, NH ₃ , Mg.	Urea + Ammono- NH ₃ , Mg.	Creat- inine, Acid, Mg.	Organic Acid, Cc.	Phos- phorus, Mg.	Non- protein Nitrogen, Mg. per Cent	Amino- Acid, Mg. per Cent	A. M.	P. M.					
														Rest, Mg.	Tenth Normal	per Cent	per Cent	
October 27.....	91	446	508	40	-102	...	73	...	26	102.1	103.0				
October 28.....	77	446	431	40	-25	...	27	...	23	102.2	102.6				
October 29.....	81	446	432	40	-26	...	38	...	23	102.2	102.7				
Average.....	83	446	457	40	-51	...	46	...	28						
Per cent of total nitrogen.....	10	...	6	103.4				
November 2.....	41	446	420	41	-15	280	37	317	6	27	1	69	24	10	5	103.4	
November 3.....	43	424	431	41	-48	285	47	332	6	27	2	64	102.4	102.2	
November 4.....	57	297	615	119	-137	431	46	447	6	31	2	99	48	52	..	103.1	103.9	
Average.....	47	389	488	67	-166	332	43	375	6	28	2	77	47	43	..			
Per cent of total nitrogen.....	68	9	77	1	6	0.4	16						
November 5*.....	38	220	346	119	-340	255	23	278	3	15	1	49	45	45	28	12	104.3	105.7
Per cent of total nitrogen.....	73	7	80	1	4	0.3	14						

* Died at 11:15 p. m.

TABLE 5.—Nitrogen Metabolism During Yellow Fever in the Case of Monkey M2

Date	Urine Vol- Weight, Kg.	Total Nitrogen			Urine Nitrogen as				Organic Acid, Phos- Tenth phorus, Mg.			Non- protein Nitrogen, Mg. per Cent		Amino- Acid, Mg. per Cent		Temperature	
		Diet, Mg.	Urine, Mg.	Stool, Balance, Mg.	Urea, Mg.	NH ₃ , Mg.	Urea + NH ₃ , Mg.	Creat- inine, Mg.	Uric Acid, Mg.	Rest, Mg.	Cc. Normal	Mg. per Cent	Mg. per Cent	Mg. per Cent	A. M.	P. M.	
November 15.....	3.42	...	365	81	102.1	103.1	
November 16.....	365	81	4	225	237	47	2	52	50	102.3	103.9	
November 17.....	...	450	300	80	69	100	100	45	2	51	35	102.7	102.8	
November 18.....	...	150	226	81	143	90	113	46	2	57	41	35	...	9	101.8	102.8	
Average.....	...	150	297	81	72	133	186	46	2	53	42			
Per cent of total nitrogen.....	53	62	15	0.7	18							
November 19.....	...	430	305	17	108	182	209	16	2	42	36	102.6	102.8	
November 20.....	...	450	247	18	185	122	146	46	2	18	35	102.1	103.3	
November 21.....	370	17	63	217	237	53	2	67	50	102.1	103.6	
November 22.....	...	385	308	18	59	186	195	45	2	60	23	104.1	104.1	
November 23.....	...	445	672	17	-214	480	510	60	4	89	102.9	102.9	
November 24.....	3.46	225	475	18	-208	285	328	50	4	87	...	29	13	8	101.7	102.3	
Average.....	...	400	414	17.5	-31	257	286	52	3	66	34			
Per cent of total nitrogen.....	62	69	12	0.7	16							
November 25.....	...	445	630	138	-323	339	420	60	6	135	44	102.2	105.1	
November 26.....	...	0	(450)†	138	-583	185	278	59	9	92	189	104.9	106.6	
November 27.....	55#	9	26	
Average.....	...	222	540	138	-450	262	349	59	7	113	116	67#	10	28	98.0	
Per cent of total nitrogen.....	48	65	11	1	21							

* Urine lost. Figures not included in average.

† Nonprotein nitrogen.

‡ Died at 10:15 a. m.

§ Blood taken at 8 a. m.

Blood taken at 10:30 a. m.

AMINO-ACID INJECTION EXPERIMENTS

The ability of a hepatectomized dog to dispose of injected amino-acid has been investigated by Bollman, Mann and Magath.² They found in those animals in which the kidneys remained, a decrease in urea nitrogen of the blood and urine and large increases in amino-acid nitrogen. Only a fraction of the amino-acid nitrogen injected was excreted in seven or eight hours following the injection. They concluded that no deaminization occurred in animals after removal of the liver.

Yellow fever at post mortem presents a striking picture of liver degeneration. How soon and to what extent this degeneration occurs probably depends on the rapidity of the onset and the final outcome of the disease. As an attempt to supplement our previous work and to demonstrate as clearly as possible a loss of ability to deaminate amino-acids in yellow fever, the following experiments were carried out.

Two animals were given injections of glycine solution and the changes in blood and urine nitrogen studied. Glycine was used, since it was the only amino-acid available. Both of the animals used for this purpose developed a fever and showed some evidences of illness, but recovered. Each monkey received 250 mg. of glycine nitrogen intravenously on two separate occasions, once during the preliminary control period and again during the fever of yellow fever. Blood and urine were studied before and at frequent intervals after the injections. In neither case did the reactions during the febrile periods differ appreciably from those during the control periods.

Metabolism Study of a Monkey That Died of a Febrile Disease of Unknown Etiology.—As a basis of comparison with yellow fever, a nitrogen study of a monkey which died after a fever of unknown etiology (autopsy revealed some pneumonia) is included.

EXPERIMENT 6.—*Macacus rhesus* M6, a large female, apparently in good condition, was fed on diet no. 3, beginning on January 18, and the metabolism studies were begun on January 23. No feces were passed from January 21 until January 25, at which time a light yellow stool, about the size of a large kidney bean and of firm consistency, was passed; the monkey vomited 20 cc. of the diet and appeared ill and generally weak, showing rapid shallow respiration.

On January 26, the animal vomited; a slight diarrhea occurred. The condition was the same as on January 25. On January 28, there was violent diarrhea and the urine was grass green in color. On January 29, the diarrhea continued, and the monkey died suddenly without the signs of prostration that precede death from yellow fever.

The urine and blood analysis are recorded in table 6.

2. Bollman, J. L.; Mann, F. C., and Magath, T. B.: *Am. J. Physiol.* **78**:258, 1926.

TABLE 6.—*The Nitrogen Metabolism of Monkey M6 with a Fatal Illness of Unknown Origin*

Date	Urine Volume, Cc.	Urine Nitrogen as					As per Cent Total Nitrogen					Blood Nitrogen as		Temperature					
		Total, Mg.	Urea, Mg.	NH ₃ , Mg.	Urea + NH ₃ , Mg.	Amino-Creat-Acid, inine, Mg.	Rest, Mg.	Urea, Mg.	NH ₃ , Mg.	Urea + NH ₃ , Mg.	Amino-Creat-Acid, inine, Mg.	Rest, Mg.	Non-protein Nitrogen, Mg. per Cent	Urea, Mg. per Cent	Amino-Acid, Mg. per Cent	A. M.	P. M.		
January 23.....	101	547	339	37	376	8	54	169	62	7	69	1	10	20	101.8	102.1	
January 24.....	36	635	455	43	493	6	43	88	72	7	79	1	7	13	102.7	103.1	
January 25.....	60	1,165	890	90	980	9	61	115	76	8	84	1	5	10	102.9	104.5	
January 26.....	59	1,174	842	83	930	11	57	176	72	7	79	1	5	15	41	18	7	102.9	104.9
January 27.....	58	1,110	765	75	840	10	60	200	69	7	76	1	5	18	103.2	103.9
January 28*	25	11	6	101.5	103.1
January 29†	35†	12	9	101.1	102.5

* Violent diarrhea. Urine contaminated.

† Died at 4:30 P. M.

‡ Blood taken five minutes post mortem.

COMMENT

The excretion of uric acid appears to increase slightly during the last few hours of life (tables 2 to 5, inclusive). However, these increases are small, corresponding in magnitude to those observed in the blood,¹ and do not indicate any grave injury to uricolytic function. The quantities excreted during the control periods are in agreement with those reported by Hunter and Givens.³ Although in some experiments the uric acid output became from two to four times the normal, the total changes amounted to only a few milligrams at the most and are not of the same magnitude as those observed by Mann and his associates.⁴ In hepatectomized dogs which they studied, uric acid appeared in the urine in such high concentration that it formed a heavy flocculent precipitate.

Attention has already¹ been called to species differences in the metabolism of uric acid. Although the power of uricolysis is not usually attributed to human liver, Quincke⁵ found enormous quantities of uric acid in the urine of patients who had recovered from acute yellow atrophy of the liver. In Rabinowitch's⁶ case, however, blood uric acid remained normal, and no appreciable quantities were found in the urine. According to Wells,⁷ the liver of *Macacus rhesus* is the only organ of that animal which is capable of destroying uric acid in vitro. If this is true also of the living animal, and if, as Mann⁸ has pointed out with regard to the dog, "the destruction of uric acid is the most easily injured known function of the liver with relation to metabolism," accumulation and excretion of uric acid in monkeys with yellow fever should be far greater than any observed. Either uricolysis in monkeys is not so easily disturbed by the hepatic lesions of yellow fever, or it is a function not confined exclusively to the liver.

Creatinine excretion was remarkably constant from day to day during control periods. A rise of temperature was always accompanied or preceded by an increase of urinary creatinine. The quantities excreted roughly paralleled the temperature, and the peak of the fever was usually accompanied by the maximum creatinine output. The minimal accumulations of creatinine in the blood,² in the face of increased creatinine excretion, indicate neither severe renal damage nor distur-

3. Hunter, A., and Givens, M. H.: J. Biol. Chem. **13**:371, 1912-1913; *ibid.* **17**:37, 1914.

4. Bollman, Mann and Magath (footnote 2).

5. Quincke in Nothnagel: *Specielle Pathologie und Therapie*, Vienna, vol. 18.

6. Rabinowitch, I. M.: J. Biol. Chem. **83**:333, 1929.

7. Wells, H. G.: J. Biol. Chem. **7**:171, 1910.

8. Mann, F. C.: *Modifying Physiologic Processes Following Total Removal of the Liver*, J. A. M. A. **85**:1472 (Nov. 7) 1925.

bance of creatinine production. Mann and his co-workers² found that the excretion of creatinine in dogs was not appreciably affected by hepatectomy.

In the control periods, ammonia nitrogen in the urine formed a rather high proportion of the total nitrogen excreted. Only in the case of the monkey M1 was it as low as 4 per cent of the total nitrogen. In the other monkeys it averaged between 7 and 10 per cent. During the febrile and terminal periods, the ammonia as a rule increased at the expense of urea nitrogen. In M 1, M 5 and M 2 (tables 2, 3 and 5) the ammonia output during the height of the fever became from three to four times the normal average. Monkey M 4 (table 4) had a higher output during the control period than during the yellow fever period. In the monkey M 5 (table 3), ammonia nitrogen formed 22 per cent of the total nitrogen during the last two days of life.

This increased output of ammonia may be ascribed to the larger output of organic acid and phosphorus during the illness. Bollman, Mann and Magath² found the ammonia excretion during the first six hours after dehepatization to be about three times greater than normal.

The amounts of organic acids and phosphorus in the urine did not parallel the total nitrogen excreted but were usually largest on the last day of life regardless of any decline in the nitrogen excretion. In monkeys M1, M5 and M2 (tables 2, 3 and 5), the organic acid and phosphorus excretions had increased during yellow fever from two to five times the normal amount, while in M4 (table 6) they were higher during the control period. Roman⁹ considers that the increased ammonia excretion reported during acute yellow atrophy is probably due to the presence in the urine of organic acids, which were identified as sarcolactic, oxymendelic, acto-acetic and β -oxybutyric acids. The organic acids in yellow fever are presumed to be acid products of protein autolysis. There seems to be no relationship between the amounts of organic acid and rest nitrogen excreted.

Briefly stated, the ammonia nitrogen of the blood does not change noticeably during yellow fever, while the amount excreted in the urine does increase at the expense of urea nitrogen. This increase in urinary ammonia is coincident with larger excretions of organic acid and phosphorus. The organic acids and phosphorus in the urine increase during the febrile and terminal periods without apparent relationship to the amount of rest nitrogen.

Alterations in amounts and proportions of urea and amino-acid nitrogen fractions of blood during yellow fever present a picture suggestive of loss of the deaminizing and urea-forming functions of

9. Roman, B.: Acute Yellow Atrophy of the Liver, *Arch. Path.* 4:399 (Sept.) 1927.

the liver. The quantities and proportions of the two fractions in the urine do not, at first sight, support such a conclusion. The excretion of urea, ammonia, amino-acids and rest nitrogen during yellow fever presents no striking features. Normally, in spite of the controlled nitrogen intake, the amount of nitrogen in the urine from day to day was far from constant. The amount of total nitrogen excreted invariably increased during fever indicating a toxic destruction of protein. *Macacus rhesus* M6 (table 6), during a fever of unknown origin, had the same large increase in nitrogen excretion as was displayed in yellow fever. The monkeys were in positive nitrogen balance during the control periods and gained weight. The large increases in nitrogen output, together with a reduced tolerance for the diet during illness, brought about a negative balance during yellow fever accompanied by losses in weight.

The increase in urine nitrogen during the febrile period consisted largely of urea, ammonia, and in some cases, rest nitrogen. The gain in amino-acid, uric acid and creatinine, while large in proportion to the normal excretion, contributed little to the total febrile increment. The rest nitrogen was unusually irregular, sometimes being larger and sometimes smaller during the illness. The urea nitrogen normally formed a rather low percentage of the total nitrogen. In M5 (table 3), it averaged only 49 per cent during the control period when the monkey was being fed 1.2 Gm. of protein per kilogram of body weight daily. While the proportion of urea excreted by the other monkeys studied was higher, it fell short of figures given for human beings on the same relative amounts of protein. Although the ammonia nitrogen in the urine was fairly high, it still did not compensate for the low urea output, and the urea plus ammonia nitrogen was low. For analysis of deamination and urea formation, of course, urea nitrogen + ammonia nitrogen should be considered as a single component.

The absolute quantities of urea + ammonia in the urine do not usually diminish. In fact, they usually increase. When they do decrease, it is only in the last hours of life when general diminution of nitrogen excretion indicates failure of renal function. Nor does urinary urea + ammonia invariably decrease in proportion to total nitrogen. In the cases presented, the proportion of urea and ammonia fell in monkeys M 1 (table 2), M 2 (table 5) and M 3 (table 1), but rose in M 4 (table 4).

Analysis of the urinary data, therefore, appears to contradict the conclusions drawn from the blood studies. However, the activity of the functions which are under examination, deamination and urea formation, cannot be estimated from either the rate of accumulation of urea and amino-acids in the blood or from their excretion in the urine, but

only from the rates of production and destruction of these substances in the body. This is measured by the sum of the nitrogen which accumulates in the blood plus that which is excreted in the urine.

Attempts to evaluate the rate of production and destruction of the various nitrogenous constituents have been made and are illustrated in charts 1 and 2. The production (or the resultant of production minus destruction) of any constituent must be represented by the quantity which accumulates in the body plus the amount found in the excreta. It has been assumed for purposes of calculation that at least the most important nitrogenous components, amino-acids and urea, are equally

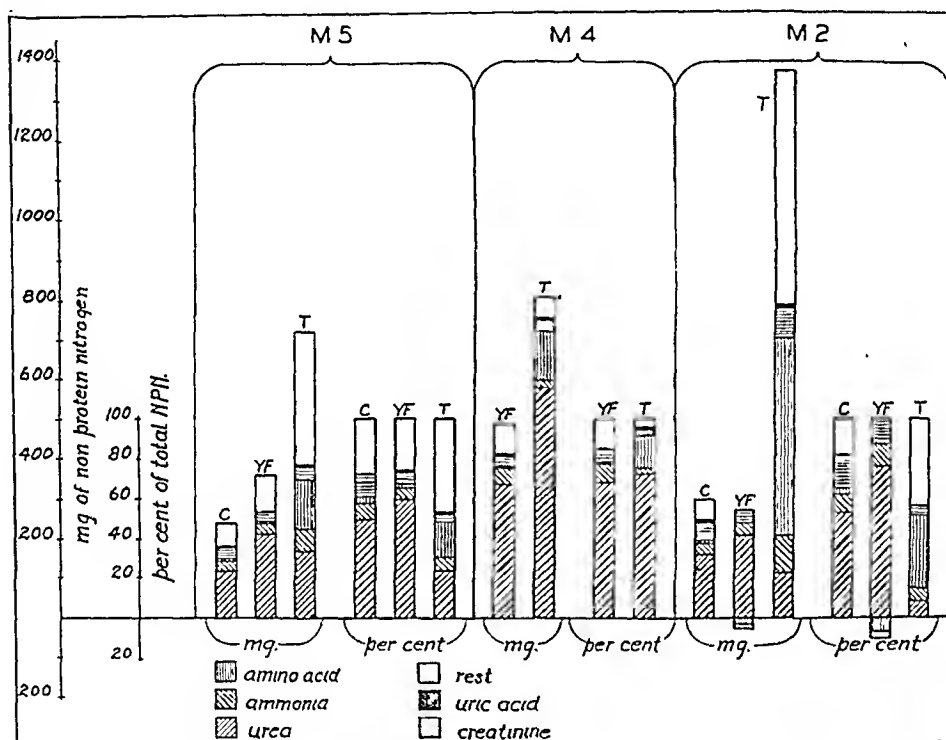


Chart 1.—The actual and relative rates of production of total nonprotein nitrogen and its components during normal control periods, C, the course of yellow fever, YF, and the premortal stage, T, calculated on monkeys M5, M4 and M2 by methods described in the text. Actual rate of production is indicated by the columns enclosed in the brackets marked "mg.," relative rate of production by the columns marked "per cent." In two cases the columns are extended below the base line. In these instances, reductions of the concentrations of the substance in the blood with unchanged or diminished urine excretion indicated actual disappearance, if not destruction, of the particular constituent. This could be expressed graphically only as negative production.

distributed throughout the fluids of the body in the same concentrations in which they appear in the blood and that 70 per cent of the body weight is fluid. The quantity of any nitrogenous component produced in a given interval, therefore, is obtained by adding to the amount found in

the urine a value equal to the change of concentration of the same substance in the blood multiplied by 70 per cent of the body weight. This method of calculation may be illustrated by an example. See Table 7.

The figures used in chart 1 for the terminal period of monkey M 2 were obtained in the following manner. The blood from this monkey on November 24 contained 29 mg. of total nonprotein nitrogen; 13 mg. of urea nitrogen and 8 mg. of amino-acid nitrogen, normal values. It

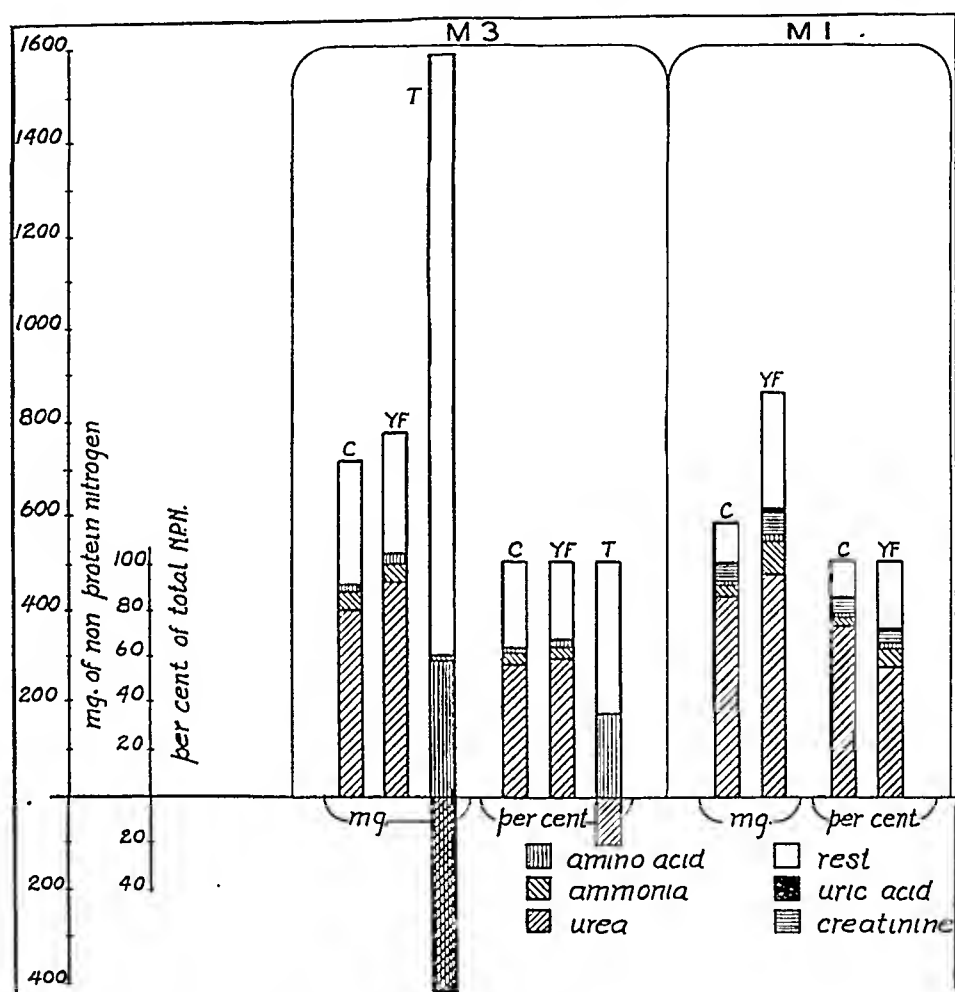


Chart 2.—Same data as shown in chart 1, calculated on monkeys M3 and M1. In the case of M3, the T column of actual production has a confusing appearance because the existence of a large negative urea production necessitates extension of the positive amino-acid production below the line to overlap the urea column.

was, therefore, assumed that uric acid and creatinine were also normal, and average normal concentrations for these substances (table 1 of preceding article) were used in the calculations. Blood withdrawn just after death contained significantly larger amounts of all nitrogenous components except urea and uric acid, both of which had fallen slightly. The monkey weighed 3.46 Kg. on November 24, and it is assumed that his weight remained constant until death; 70 per cent of 3.46 Kg. =

2,420 cc. The output of the various nitrogenous constituents is given in table 5. The data from other experiments are given in abstract form in table 8.

Since only insignificant amounts of ammonia nitrogen are found in the blood they have been neglected. The values for total production which are given in column 6 are used in constructing the figures.

TABLE 7.—*Terminal Period in Monkey M2**

	1	2	3	4	5	6
	In Blood at Death, Mg. per 100 Cc.	In Blood on Nov. 24, Mg. per 100 Cc.	Change Between 1-2, Mg. per 100 Cc.	Accumulation in Body = 3 × 24.2, Mg.	Amount in the Urine in Last 24 Hours,* Mg.	Total Production, 4 + 5
Total nonprotein nitrogen..	67	29	38	920	450	1,370
Urea nitrogen.....	10	13	-3	-73	185	112
Ammonia nitrogen.....	93	93
Amino-acid nitrogen.....	28	8	20	484	12	496
Uric acid nitrogen.....	0.24	0.29	-0.03	-0.7	9	8
Creatinine nitrogen.....	0.98	0.51	0.47	11.4	59	70
Rest nitrogen.....	28	7	21	508	92	600

* The nature of the results is quantitatively, but not qualitatively, altered if the average excretion for the last two days is used for purposes of calculation.

TABLE 8.—*The Total Production of Nonprotein Nitrogen Constituents During Yellow Fever**

Monkey	Period	Nitrogen Excreted in Urine as				Estimated Accumulation of Nitrogen in Body Fluids as				Total Nitrogen Produced in per Cent of Nonprotein Nitrogen as		
		Non-protein Nitrogen, Mg.				Non-protein Nitrogen, Mg.				Urea + NH ₃		
		Urea + NH ₃	Amino- Acid	Rest,†	‡	Urea, Mg.	Amino- Acid, Mg.	Rest, Mg.	§	Urea + NH ₃	Amino- Acid	Rest
M3	Control.....	715	435	13	268	61	2	37
	Yellow fever	774	496	20	258	64	3	33
	Terminal....	25	8	1	16	1,570	-420	700	1,290	-26	44	82
M1†	Control.....	581	449	7	125	77	1	22
	Yellow fever	860	540	15	304	168§	63	2	35
M5	Control.....	238	139	9	91	58	4	38
	Yellow fever	357	234	7	114	-141§	65	2	33
	Terminal....	237	170	5	62	482	52	121	310	31	17	52
M4	Control.....	457
	Yellow fever	488	375	6	107	77	1	22
	Terminal....	346	278	3	65	458	317	123	18	74	16	10
M2	Control.....	297	186	9	101	62	3	35
	Yellow fever	414	286	6	122	-145	-48	-24	-73	88	-7	18
	Terminal....	450	278	12	160	920	-73	484	508	15	36	49

* For the calculation of the data of M5, average blood nitrogen values for normal period taken from table 1 of the preceding article (footnote 1) were employed.

† Rest nitrogen includes uric acid and creatinine.

‡ Recovered.

§ Not included in total nonprotein nitrogen.

The columns marked "C" (control) and "YF" (yellow fever) in the figures represent the average daily excretion of nitrogen during the control and yellow fever periods; for the calculation of columns "T" (terminal period), urine excretion from the last twenty-four hours only was used.

The assumption that nitrogenous metabolites are equally distributed throughout body fluids is, of course, open to serious question. However, it is the only possible means of approximating the actual production of these metabolites. Madsen,¹⁰ in studies of the distribution of non-protein, urea and rest nitrogen in the body, found more nonprotein nitrogen in muscle than in blood or other organs, both in health and in disease. Other organs held an intermediate position between blood and muscle. In nitrogen retention, the retained nitrogen was more or less evenly distributed throughout the tissues. Urea, according to Gad-Andresen, appears to diffuse equally throughout the aqueous media of the body.¹¹ Following hepatectomy, more amino-acid nitrogen has been found in muscle than in blood.² It is probable, then, that the increase of amino-acid production is even greater absolutely and in relation to that of urea and total nonprotein nitrogen than the methods of calculation here employed indicate.

From charts 1 and 2 it becomes at once evident that the actual rate of production of urea + ammonia diminished during the terminal period in three of the four fatal cases: monkey M 4 is the only exception. In one instance, monkey M 3, a large quantity of urea appears actually to have disappeared from the body without being excreted in the urine. Amino-acid production (or failure of deaminization) increased in every instance. The proportion of total nitrogen as urea + ammonia in every instance diminished, while that as amino-acid increased greatly.

That these changes are not merely those which accompany febrile illnesses in general can be seen from table 6, which shows the nitrogen metabolism and blood nitrogen of a monkey that died after a fever of unknown etiology. The total excretion of nitrogen in this case is quite as great as that of any of the monkeys with yellow fever. However, throughout the period of observation urea + ammonia makes up about the same proportion of the total urinary nitrogen, and amino-acid excretion remains constant. In the blood, amino-acids and urea remain practically constant during the last twenty-four hours of the disease. The small changes observed correspond in direction and order of magnitude to those which occur immediately after death.¹²

The metabolism studies, therefore, confirm the blood studies. In the terminal stages of yellow fever, and only in the terminal stages, deaminization and urea formation are destroyed or greatly impaired, indicating profound liver damage. To test these functions further, injection of glycine was carried out. The data from these experiments have not been presented, because they showed no departure from the

10. Madsen, S. T.: *Acta med. Scandinav. suppl.* 7:318, 1923.

11. Gad-Andresen, K. L.: *Biochem. Ztschr.* 116:266, 1921.

12. Wakeman and Morrell (footnote 1, table 4).

normal. The rise of amino-acids in the blood was followed in both instances by an increase of blood urea that was, if anything, greater during yellow fever than in the control periods. It was impossible to calculate the amount of extra nitrogen excreted as urea and ammonia, since there were considerable daily fluctuations in the amounts of urine nitrogen, and because at the times of the second injections (during yellow fever) total nitrogen excretion had begun to fall. However, it was evident that the proportion of the injected amino-acid excreted as such was quite small and approximately the same in both periods. Both monkeys recovered and neither showed any other evidences of loss of deaminizing powers. It is an unfortunate coincidence that neither of them should have developed yellow fever in a malignant form. The experiments afford additional evidence that impairment of deaminization occurs only in the most advanced stages of the disease.

The blood and urine changes occur with great speed as the disease approaches a fatal termination. This is well illustrated by the case of monkey M 3, (table 1), and even better by monkey M 2 (table 3) of the preceding paper.¹ The latter was inoculated on May 26, and on the afternoon of May 28 had a temperature of 104.6 F. At 11:30 a. m. on May 29, when the first blood sample was taken, the monkey was lying down, but he stood up when disturbed. Although the blood sugar at this time was only 34 mg. per hundred cubic centimeters, the blood nitrogen was normal. At 8:30 p. m., the animal was in a state of collapse. It had received no food all day. During this nine hour interval, the blood sugar level had fallen to 18 mg., and the blood non-protein nitrogen and its fractions had risen to the levels typical of the premortal stage of yellow fever.

Kidney Function.—Complete, or almost complete, anuria is not uncommonly observed during the last day of life, e. g., monkey M 3 (table 1). On the other hand, occasionally, as in the case of monkey M 2 (table 5), there is considerable diuresis. It has already been pointed out¹ that the decreases in the volume of urine may be related to the marked fall of blood pressure which precedes death.

The ability of the kidneys to concentrate nitrogenous metabolites, at least until the premortal period, is demonstrated by the fact that the 2.5 cc. of urine excreted by monkey M 3 (table 1), when the nonprotein nitrogen of the blood was about 66 mg. per hundred cubic centimeters, contained 25 mg. of nitrogen, or 10 Gm. per liter. The lowest concentration occurred in the case of monkey M 5 (table 3), which was 5.4 Gm. of nitrogen per liter. Even this was greater than the average for the control period, 4.9 Gm. The most concentrated urine was that of monkey M 1 (table 2), which averaged 16.5 Gm. of nitrogen per liter during the yellow fever period. Part of the terminal increase of blood nonprotein nitrogen increases are probably to be ascribed to the

extraordinarily high rate of nitrogen destruction that characterizes the disease and taxes the kidneys to the utmost. Undoubtedly, the kidneys are anatomically and functionally damaged; but this injury does not appear to be the chief factor in the production of the most characteristic functional disturbances of the disease. The ability of the kidney itself to produce urine in normal amounts and of normal concentration seems to be retained relatively intact throughout the disease.

SUMMARY

Studies of changes in the nonprotein nitrogenous substances which occur in the blood and urine of *rhesus* monkeys suffering from yellow fever are presented.

The nonprotein nitrogen, amino-acid, urea and rest nitrogen of the blood, increase by considerable amounts during the last hours of life.

Blood creatinine, uric acid and ammonia change little if at all.

Amino-acid increases both in absolute amount and in proportion to the nonprotein nitrogen, while urea decreases in proportion to non-protein nitrogen. A few cases were found in which there was an absolute decrease in blood urea nitrogen.

These changes were found to be terminal events. No significant alterations occurred during the early stages of the disease or in those monkeys which recovered.

There were no marked alterations in the partition of these substances in the urine.

The changes in the terminal period are shown to be much more pronounced when the accumulation of these substances in the body fluids is considered.

Organic acid and phosphorus excretion usually increased considerably during the disease.

The changes observed were interpreted as resulting from a loss of liver function.

No definite evidence of serious impairment of kidney function was observed, except a terminal anuria probably due to extreme reduction of blood pressure.

THE HAZARD OF INCISION FOR APPARENT QUINSY IN DIPHTHERIA *

J. E. GORDON, PH.D., M.D.

AND

D. C. YOUNG, M.D.

DETROIT

The unhappy result of mistaken diagnosis is usually limited to delay in proper treatment. At times the penalty is greater. During the past few years we have been impressed with the high fatality among patients with diphtheria after surgical incision of the peritonsillar tissues in the belief that the condition was one of peritonsillar abscess.

There are two indications for surgical intervention in diphtheria. Intubation or tracheotomy is necessary when membrane invades the larynx or trachea to such an extent as to interfere with respiration. Extraneous conditions in a patient suffering with diphtheria may require remediation, as acute appendicitis or fracture of the humerus, both of which have been seen in patients with diphtheria.

The disease is primarily a local infection of the mucous membrane of the nose, throat or nasopharynx. At the site of the lesion, a powerful exotoxin is elaborated by the invading infectious agent. This toxin passes to the blood stream by way of the lymphatics draining that region and produces a toxemia of high degree. Toxin carried by the blood may be neutralized in one of two ways. Various tissues of the body may accomplish this end, but only with resulting damage of considerable extent, particularly evidenced by tissues of the nervous and cardiovascular systems. Free toxin before union with tissue may be neutralized by artificially administered antitoxin.

Successful management of faucial diphtheria depends, therefore, on two considerations. Specific antitoxin must be administered early in the course in order that toxin entering the blood stream may be neutralized before union with tissues, thus preventing the degenerative processes which otherwise follow.

The second consideration demands that opportunity for absorption of toxin from the local lesion be limited to a minimum. Trauma evidently favors absorption, because an open lesion offers more favorable conditions than does the relatively intact mucous membrane. Largely because of this consideration, local applications to the throat in diphtheria have fallen into disrepute. The injury to tissue which followed the rather vigorous application of Loeffler's solution and similar prepa-

* Submitted for publication, Feb. 14, 1930.

* From the Herman Kiefer Hospital, Department of Health.

rations evidently did more harm than good, because of the more ready avenue for absorption of toxin which followed. In present practice, no local applications are used. So thoroughly are physicians impressed with the importance of avoiding local injury that little sympathy exists for the practice, often indulged in, of inducing bleeding of tissues covered by membrane in an attempt to distinguish a diphtheritic from a pyogenic process of the throat. That is no more necessary than feeling the lesions in smallpox. Careful inspection will serve equally well.

If it is important to avoid the minimal injury to tissue resulting from such procedures, it is quite apparent that actual surgical incision of the faucial tissues must constitute a real hazard by favoring absorption of toxin.

Our experience includes no instance in which incision of the peritonsillar space was practiced in a recognized case of faucial diphtheria. Patients in this series were received in the hospital after surgical incision resulting from confusion of the diagnosis of diphtheria with that of quinsy.

PERITONSILLAR ABSCESS SIMULATING DIPHTHERIA

The differentiation of faucial diphtheria and peritonsillar abscess may include errors in both directions; namely, cases of diphtheria may be mistaken for peritonsillar abscess, and instances of abscess may be considered diphtheria. The latter is without great medical importance, as treatment is not altered except in the matter of administering antitoxin, and that does not effect the favorable course of the disease. The only consideration is unnecessary quarantine and isolation.

During 1928 and 1929, 2,977 patients were admitted to Herman Kiefer Hospital with the diagnosis of diphtheria. This diagnosis was confirmed in 78 per cent of the total number. Certain allied conditions account for most of the other cases. Common among these were acute follicular tonsillitis, scarlet fever, Vincent's angina, peritonsillar abscess and diphtheria bacillus carriers; in the latter group, no pathologic factors were evident. The number of patients with quinsy was twenty-nine, a ratio of 1 per cent of all admissions. Total admissions to the service for patients with diphtheria together with final diagnoses are presented in the appended table (table 1).

There is no doubt that a patient with pus formation in tissues centering about the tonsil suffers from a severe type of throat infection. Certain clinical features, however, serve to distinguish this lesion from diphtheria. Patients with quinsy are usually adults, those with diphtheria, children. In contrast to the low temperatures which characterize diphtheria, the temperature in peritonsillar abscess is usually about 102 F. and may be as high as 104 F. In the severe type of faucial diphtheria which might be confused with abscess, it is more likely to be about 100 F.

theria in which the differentiation might logically be required. This proportion is unduly great. Surgical procedure in each instance followed an erroneous diagnosis of peritonsillar abscess, later recognized as true diphtheria.

Many of these cases must primarily be of the nasopharyngeal type, in which the membrane is readily discernible only by examination of the posterior surface of the uvula and the back wall of the pharynx. Membrane on the tonsils may be minimal. At any rate, swelling of the faucial tissues is apparently so great that incision of the peritonsillar space is performed in the belief that the condition is one of peritonsillar abscess. There follows a marked production of membrane, which within from twelve to twenty-four hours covers the uvula, soft palate, both tonsils, pharynx and nasopharynx, and even extends over the gingival surfaces. Two cases were seen in which there was membrane even on the buccal mucosa of the cheek. Swelling of the neck is often so extreme as to interfere with respiration. The picture is one of extreme toxemia and constitutes malignant diphtheria, if any case justifies that term. The opening of a raw incised wound at the actual site of active lesions undoubtedly leads to absorption of toxin in a degree not otherwise possible.

Whatever the ultimate outcome after peritonsillar incision, the course is invariably a stormy one. Of those who died, fatal termination usually resulted within the first few days because of the extreme toxemia and associated circulatory failure. A typical example is represented by the following instance.

CASE 1.—M. S., a white girl, aged $4\frac{1}{2}$ years, on December 28, developed a sore throat, accompanied by low grade fever and headache. She became worse progressively, the soreness of the throat being more marked on December 31. The left peritonsillar area was lanced on January 1. The patient made no improvement, and on January 2, received 15,000 units of diphtheria antitoxin. Later that day she was admitted to the hospital and received 40,000 additional units. There was, at that time, a purulent nasal discharge, and the glands of the neck were greatly enlarged and moderately tender. There was an extreme bilateral cervical lymphadenitis with periadenitis and edema of the tissues of the neck. The tongue was glazed and dry. A necrotic, grayish red, somewhat hemorrhagic membrane covered the tonsils, uvula, soft palate and posterior pharyngeal wall. The throat was moderately red, with an intense edema of the faucial tissues. A surgical incision extended from the lower part of the soft palate, on the left, down to the tonsil of that side. The borders of the heart were moderately enlarged to the left, and the first heart sound was softened. The fever was 101.8 F. by rectum, the pulse soft and indeterminate. The patient appeared to be extremely toxic; circulatory failure was progressive, and death occurred twenty-four hours after admission.

Four patients survived the acute stage of the illness to die late in the disease, about the thirty-fifth day, of multiple postdiphtheritic paralyses and ultimate respiratory failure through dysfunction of the

phrenic nerve. Among the patients who recovered there were also four who had this type of late neurologic condition, but who eventually recovered after a long stay in the hospital, in one instance after ninety-one days.

CASE 2.—W. S., a youth, aged 18, on January 14, developed a sore throat accompanied by headache and low grade fever. On January 16, the throat was lanced. No culture was taken for *B. diphtheria*. On January 18, he was given 90,000 units of antitoxin and brought to the hospital. Swelling of the neck was extreme. The membrane in the throat covered practically all visible structures. The temperature was 99.8 F. The patient continued to be extremely ill during the subsequent few days. On January 23, paralysis of the palate developed; by January 26, his condition was extremely poor and his color, ashy gray; a gallop rhythm was heard over the apex of the heart. The systolic blood pressure dropped to 85 of mercury and the diastolic to 55. His condition was precarious for the next week, but thereafter the circulation improved. Unfortunately, successive paralyses of the peripheral nerves involved the palate, the pharynx and the larynx. Eventually,

TABLE 2.—*Fatality in Diphtheria After Peritonsillar Incision, Compared with the General Fatality from Diphtheria, by Age Groups*

Age, Years	Cases	Deaths	Fatality, per Cent	Fatality in All Types of Diphtheria, per Cent
0 to 4	3	3	100.0	25.0
5 to 9	7	4	57.0	14.2
10 to 14	2	1	50.0	5.3
15 to 19	6	4	67.0	2.0
20 to 29	16	8	50.0	5.1
30 to 39	6	3	50.0	4.0
40 to 49	2	1	50.0	14.2
50 to 59	1	1	100.0	12.5
Total.....	43	25	58.0	12.9

all four extremities were involved, and on February 18, paralysis of the phrenic nerve occurred with consequent respiratory embarrassment. The heart failed under this strain. The patient was irrational on February 23; circulatory failure became more pronounced with a return of gallop rhythm, and marked coldness and numbness of the extremities followed. The patient died on February 24, thirty-seven days after admission to the hospital.

The fatality in these conditions reaches unprecedented levels. Twenty-five of forty-three patients died, giving a fatality of 58 per cent. Among patients with diphtheria of equal severity other than for the factor of incision, whose membrane was just as extensive and who had received antitoxin for the first time at essentially the same stage of the disease, the fatality was 34 per cent. The fatality for diphtheria of all types during the period considered was 12.9 per cent. The hazard of incising the throat in diphtheria would thus appear to be real. It is greater than the actual data indicate, because most of these patients were in advanced age groups, which have a fatality measurably less than that for young children. This is well illustrated by the accompanying table (table 2).

Perhaps the most important deduction from analysis of these forty-three case records of peritonsillar incision in diphtheria is the conclusive demonstration that when antitoxin is given shortly after the incision is made, the fatality is far less than if administration is delayed twenty-four hours or more. Antitoxin was administered to nineteen patients within twenty-four hours of the time of operation, although in some instances in small amounts only. The fatality was 35 per cent, which corresponds almost mathematically with the fatality for patients with diphtheria of approximate severity when incision was not practiced, namely, 34 per cent. The remaining twenty-three patients were given antitoxin at a later period, in all instances twenty-four hours or more after operation, and in one instance three days. The fatality in this group was 77 per cent. These data tend to corroborate our hypothesis that the facility of toxin absorption provided by the open wound accounts for the remarkably high fatality. The incision itself, however, does not markedly affect the ultimate result if the error is immediately compensated by injection of diphtheria antitoxin.

The delayed administration of antitoxin does not of itself account for the greatly increased fatality in these cases. Careful comparison with control cases of equal severity and essentially the same duration in days demonstrates an almost identical fatality in the two groups, provided antitoxin was given within twenty-four hours of the time the surgical incision was made.

So far as can be demonstrated, no increase in fatality through increased opportunity for absorption of toxin follows tracheotomy or the less definite trauma attendant on intubation of the larynx. Why, then, the danger from operative procedure in the peritonsillar region? The answer is that tracheotomy and intubation are performed with the diagnosis of diphtheria definitely made, and administration of antitoxin has preceded or immediately follows the operation. Under similar conditions, we have shown that little added risk accompanies peritonsillar incision. The danger is in delaying the administration of antitoxin. Of minor importance is the fact that lymphatic drainage from the larynx and trachea is less rich than from the pharynx and nasopharynx.

The high fatality in this group occurred despite energetic treatment. Larger amounts of antitoxin than usual were given because of the recognized severity of the illness from which these patients were suffering. Two patients received 90,000 units of antitoxin, five received 80,000, and the usual dose was from 60,000 to 70,000 units. Many patients were given serum intravenously.

The one important recommendation that we would make is that whenever a supposed peritonsillar abscess is incised without delivery of pus antitoxin be administered immediately. If the condition actually

DEMONSTRATION OF LOCAL IMMUNITY OF THE PERITONEUM BY MEANS OF THE SHWARTZMAN PHENOMENON *

IRVING A. FRISCH, M.D.

NEW YORK

The conception of local immunity, i.e., the locally increased resistance of a tissue or organ without the participation of the organism as a whole, is not a new one. It has long been recognized that the tissue cell, as the ultimate functional body unit, must be the source from which originate the various protective constituents of normal and immune serums, and that it must be in these cells that the primary changes of the processes known as immunization take place. In support of this view there are both clinical and experimental data; of the former, one notes, for example, the occurrence of crops of furuncles in widely different parts of a patient's skin, one crop healing only to have another crop arise; there the process of limitation and healing of the infected foci is surely not due to any generalized resistance, but rather to local causes. On the experimental side there is, among others, the work of Romer¹ on abrin immunization of the conjunctiva; of Kraus and Volk² on the demonstration of the corneal immunity against vaccine virus; of Wassermann and Citron,³ who demonstrated the lowering of the antibody content of the blood immediately following the removal of the local source of production. Besredka⁴ and his followers attempted to explain the phenomena of local immunity on the basis that for each disease there is a certain vulnerable receptive tissue which acts as the normal portal of entry for the virus, and that the protection is conferred on the individual by the local immunization of the specific portal of entry, irrespective of any generalized reaction by other cells in the body. In Europe, especially France, his principles have been applied in the subcutaneous vaccination against anthrax, and also, to a lesser extent, in the prophylactic immunization by mouth against typhoid, paratyphoid, cholera and bacillary dysentery. Gay,⁵ in a review of the subject, stated that Besredka's explanations of the

* Submitted for publication, Dec. 17, 1929.

* From the Laboratories of the Mount Sinai Hospital.

1. Romer, P.: Arch. f. Ophth. **52**:72, 1901.

2. Kraus, T., and Volk, R.: Wien. klin. Wchnschr. **19**:620, 1906.

3. Wassermann, A., and Citron, J.: Ztschr. f. Hyg. **50**:331, 1905.

4. Besredka, A.: Local Immunization (translated by Harry Plotz), Baltimore, Williams & Wilkins Company, 1927.

5. Gay, F. P.: Local or Tissue Immunity, Arch. Path. **1**:590 (April) 1926.

observed facts are not wholly acceptable. He nevertheless affirmed his belief in the existence of a truly localized form of immunity. Steinberg and Goldblatt,⁶ and later Herrmann,⁷ showed by means of experiments on animals that intraperitoneal injections of streptococcus and colon bacillus vaccine were of definite value in affording protection against fecal soiling of the peritoneum.

In order to demonstrate further the occurrence of local peritoneal immunity, I have employed a phenomenon of local skin reactivity to certain bacterial culture filtrates, first described by Schwartzman⁸ in 1928, and confirmed by Hangar⁹ and by Ecker and Welch¹⁰ (the latter investigators using the term Schwartzman phenomenon). A rather complete description of this phenomenon is essential in order to understand fully the following experiments. Schwartzman's original work was done with a culture filtrate of *B. typhosus*. The injection of 0.25 cc. of such a toxic substance into the abdominal skin of a normal rabbit will produce no reaction, except perhaps a mild erythema. (It is worthy of note that different areas of skin of the abdomen of the same rabbit may present considerable variations in the intensity of the primary erythema produced by injection into the skin of *B. typhosus* culture filtrate.) If, then, after a period of twenty-four hours one injects as little as 0.01 cc. of the toxic substance per kilogram of body weight intravenously, there is produced within two hours after the injection a blue discoloration at the site of the previous injection into the skin; this discoloration increases rapidly, until at the end of four hours it is extremely pronounced as a dark blue central area with a deep red zone at the periphery; the skin over these hematomas is glossy and smooth.¹¹ Histologic sections of such a hemorrhagic area show a severe type of hemorrhage and necrosis, with edematous skin, ruptured blood vessels, engorged subcutaneous tissue, extensive leukocytic ingestion and pronounced necrobiosis of these cells both inside and outside of the blood vessels.

6. Steinberg, B., and Goldblatt, H.: Peritonitis: IV. Production of Active Immunity Against the Fatal Outcome of Experimental Fecal Peritonitis, Arch. Int. Med. **42**:415 (Sept.) 1928.

7. Herrmann, S. F.: Experimental Peritonitis and Peritoneal Immunity, Arch. Surg. **18**:2202 (May) 1929.

8. Schwartzman, G.: Proc. Soc. Exper. Biol. & Med. **25**:560, 1928; J. Exper. Med. **48**:245, 1928; Proc. Soc. Exper. Biol. & Med. **26**:131, 1928; J. Exper. Med. **49**:593, 1929; Proc. Soc. Exper. Biol. & Med. **26**:207, 1928; *ibid.* **26**:843, 1929; J. Infect. Dis. **45**:283, 1929; J. Exper. Med. **50**:513, 1929; *ibid.*, to be published.

9. Hangar, F. M.: Proc. Soc. Exper. Biol. & Med. **25**:775, 1928.

10. Ecker, E. E., and Welch, H.: J. Exper. Med. **51**:409, 1930.

11. The factors which induced the local skin reactivity are termed "Skin Preparatory Factors" and those involved in production of local hemorrhagic reactions following the intravenous injections, "Reacting Factors."

This reaction may be produced in as high as 85 per cent of rabbits into which injections are made. The intensity and size of the local hemorrhagic reactions are in no way related to the intensity of the erythema produced by the preparatory injection into the skin; animals that show no primary erythema may show a very strong hemorrhagic reaction after intravenous injection, and, conversely, animals that show a marked primary erythema may not react at all to the intravenous dose. That the local trauma produced by the preparatory injection into the skin is not in itself responsible for the localization of the toxic factors introduced intravenously is evidenced when one injects non-specific irritating substances (turpentine or sterile tryptic digest broth) into the skin in place of *B. typhosus* filtrate. Under such conditions the intravenous injection of *B. typhosus* culture filtrate is not followed by any reactions. Moreover, if instead of injecting the second dose intravenously, one makes another injection into the original area twenty-four hours later, no hemorrhagic necrosis is produced; instead there is only a pronounced reddening of the skin, shown histologically by a marked cellular infiltration without, however, any breaking up of the cells or damage to the blood vessels. Furthermore, if the secondary intravenous injection should be given before fifteen hours or after thirty-two hours, no hemorrhagic reaction results. Thus there is in the phenomenon an entirely new reaction the main features of which are: (a) local skin reactivity; (b) a definite short incubation period necessary to induce this reactivity (from eighteen to thirty-two hours); (c) a short duration of the state of this reactivity; (d) the ability to induce local reaction by a single skin injection, and (e) the necessity to make the second injection of the toxic substance by the intravenous route. In attempting to modify this last condition, I tried various other ways of introducing the toxic substance into the body.

ATTEMPT TO MODIFY THE SHWARTZMAN PHENOMENON

Methods.—The toxic substances used were prepared as follows: (a) Two hundred cubic centimeters of tryptic digest broth were added to 2,000 cc. Erlenmeyer flasks to give a large surface area. The entire growth of one 24 hour old agar slant culture of *B. typhosus* (strain T_L) was suspended in 10 cc. salt solution. Ten cubic centimeters of the suspension was added to each Erlenmeyer flask. The cultures were then filtered through paper and cotton and finally through Berkefeld V candles. The filtrates were tested for sterility and then titrated as to their toxicity by means of the typical Shwartzman reaction. It was found that they would give positive reactions in about 75 per cent of the animals tested if one used as the intravenous dose 2 cc. per kilogram of the body weight of the rabbit. This toxic substance was labeled T_L 527. (b) Each of four Kolle flasks was inoculated with the entire growth of one 24 hour old agar slant of *B. typhosus* (strain T_L) which had been suspended in 4 cc. of salt solution. After an incubation period of twenty-four hours, the surfaces of the colonies in each flask were washed with 10 cc. broth and these washings were placed on the sur-

face of Kolle flasks, 3 cc. for each flask. After another incubation period of twenty-four hours the surfaces of the flasks were again washed with 12 cc. of saline each. The cultures were then tested for sterility, filtered through Berkefeld V candles and again tested for sterility. The toxic substance thus obtained was tested by means of the Shwartzman phenomenon and found to give positive reactions in about 80 per cent of the animals, when one used as the intravenous dosage as little as 0.2 cc. per kilogram of body weight of the rabbit. This toxic substance was labeled A_8 .

Experimental Work.—Protocol 1: Five-tenths cubic centimeters of filtrate $T_L 527$ was injected into the upper and lower right and left areas of the skin of the abdomen of eight rabbits. Twenty hours later 12 cc. of the filtrate per kilogram of body weight was fed by mouth to each rabbit. In none of these rabbits was the typical hemorrhagic reaction obtained at the site of the original skin injection. These experiments were repeated, only this time the skin incubation period was shortened to fourteen hours to allow for the slower absorption period from the gastro-intestinal tract. The results, however, were all negative.

Protocol 2: Five-tenths cubic centimeters of filtrate $T_L 527$ was injected into the upper and lower right and left areas of the skin of the abdomen of eight rabbits. Twenty hours later 8 cc. of the filtrate per kilogram of body weight was injected into the thigh muscles of each of eight rabbits. In none of these rabbits was any hemorrhagic reaction produced. This experiment was also repeated; this time 10 cc. of the filtrate per kilogram of body weight was used, with a skin incubation period of fifteen hours. The same negative results were obtained.

In order to determine whether any substance in the muscle itself was responsible for the prevention of the reaction, extracts of ground muscle were mixed with some of the culture filtrate before the filtrate was injected into the rabbits' abdominal skin; twenty-four hours later the culture filtrate was injected intravenously into these rabbits, and typical hemorrhagic reactions were obtained at the site of the preliminary injection.

Protocol 3: Five-tenths cubic centimeter of culture filtrate $T_L 527$ was injected into four areas of the abdominal skin of twelve rabbits. Twenty-four hours later each of these rabbits was given 6 cc. of the filtrate ($T_L 527$) per kilogram of body weight intraperitoneally. Four hours after the intraperitoneal injections had been made, blue discolorations appeared at the site of the previous skin injections in four animals. The discolorations observed rapidly increased until in about six hours the reaction became extremely pronounced, the areas being dark blue in the center with deep red zones at the periphery.

A repetition of the foregoing intraperitoneal experiment, this time using twelve rabbits and allowing only eighteen hours for a skin incubation period, gave positive results (hemorrhagic reactions at the site of the original skin injection) in six rabbits.

Another repetition of the experiment, allowing a skin incubation period of twenty hours and using 3 cc. of the filtrate per kilogram of body weight, gave a positive reaction in one of eight rabbits so treated.

As is seen from the foregoing protocols, the phenomenon of local skin reactivity to *B. typhosus* can be produced by intraperitoneal, as well as by intravenous, injection of the same filtrate.

It was not possible to produce this phenomenon, however, when the second injection was introduced orally or intramuscularly. Just why

these methods failed to produce the reaction is not fully clear, as eventually the toxic substance must be absorbed into the blood stream. As was noted, muscle extract, when mixed with the filtrate and injected into the skin, failed to inhibit the reaction when done by the intravenous method.

THE DEMONSTRATION OF LOCAL TISSUE IMMUNITY

On the basis of the fact noted, namely, that the Shwartzman phenomenon could be elicited by introducing the reacting factors by the intraperitoneal route as well as by the intravenous route, the following experiments were performed.

Method.—One-tenth cubic centimeter of the *B. typhosus* filtrate A_8 was injected into each of four areas of the abdominal skin of thirty rabbits. Twenty hours after the preliminary skin injection each rabbit received 0.5 cc. of this culture filtrate per kilogram of body weight intraperitoneally. (A previous titration had shown that 0.3 cc. of this toxic substance per kilogram was sufficient to produce a positive reaction as evidenced by marked hemorrhagic necrosis at the site of the initial skin inoculation.) It was then attempted to immunize these fourteen positive rabbits against the toxic substance of *B. typhosus*. (For the purpose of immunization the less powerful toxic substance, $T_L 527$, was used, the minimum titrated intraperitoneal dosage of which was 4 cc. per kilogram of body weight.) These fourteen rabbits were then divided into four groups.

Group 1 (Two Rabbits): These rabbits received no further immunizing dose, but five days after the initial intraperitoneal injection they were again tested in a similar manner (*B. typhosus* culture filtrate A_8 , 0.1 cc. into the abdominal skin, followed in twenty hours by 0.5 cc. per kilogram of body weight intraperitoneally) and were found still to react in a markedly positive manner.

Group 2 (Two Rabbits): Three days after the initial intraperitoneal dose, these animals received a second intraperitoneal injection of *B. typhosus* culture filtrate (4 cc. of culture filtrate $T_L 527$ per kilogram of body weight). After four more days, they were retested in the original manner with the *B. typhosus* culture filtrate A_8 and positive reactions were still obtained.

Group 3 (Eight Rabbits): These animals received an intraperitoneal injection of *B. typhosus* culture filtrate, $T_L 527$, every third day, the dosage varying from 4 to 6 cc. per kilogram of body weight, in all five injections. Two rabbits died during the course of these inoculations. Three days after the last inoculation the remaining six rabbits were again tested by means of the preliminary skin dose of 0.1 cc. of culture filtrate A_8 followed in twenty hours by an intraperitoneal dose of 0.5 cc. of the same substance per kilogram of body weight. All of these rabbits, which previously had reacted to the intraperitoneal injections in a positive manner, i. e., a hemorrhagic necrosis occurred at the site of the original inoculations, were found to be negative, i. e., they gave no cutaneous reaction. Two days following this, the process was repeated, only this time the second dose of culture filtrate was given intravenously. For the intravenous dose the amount of filtrate A_8 used was 0.2 cc. per kilogram of body weight. Three of the six rabbits showed markedly hemorrhagic necrotic reactions at the site of the cutaneous inoculations; one gave a completely negative response, and the other two showed weakly positive reactions at the site of the preliminary skin injection.

Group 4 (Two Rabbits): These rabbits were given injections in a similar manner to those in group 3, except that they received six intraperitoneal injections of T_L 527. The result of the intravenous retest showed a markedly positive reaction in one, while in the other the abdominal areas remained unchanged.

It is thus seen that of the fourteen rabbits in which a skin reactivity was induced on the introduction of the toxic substance intraperitoneally, the last two groups, which received from five to six intraperitoneal immunizing doses, were rendered negative to a repetition of this reaction. Following this, however, when the toxic substance was introduced into the previously prepared animals intravenously, the typical local hemorrhagic reaction was found to be present in six animals, being markedly positive in four of these, weakly so in two and entirely absent in only two animals.

Demonstration of Local Peritoneal Immunity

Number of Rabbits	Skin Reactions at Previously Prepared Sites, After Intraperitoneal Injection of <i>B. Typhosus</i> Culture Filtrate*	Number of Intraperitoneal Injections of <i>B. Typhosus</i> Culture Filtrate†	Retesting of Rabbits Susceptible to Shwartzman Phenomenon Using <i>B. Typhosus</i> Culture Filtrate, Introduced Intraperitoneally*	Retesting of Rabbits Susceptible to Shwartzman Phenomenon Using <i>B. Typhosus</i> Culture Filtrate, Introduced Intravenously†
1	++++ (hemorrhagic)	5	0 (negative)	++++
2	++++	5	0	++
3	++++	5	0	++
4	++++	5	0	++++
5	++++	5	0	0
6	++++	5	0	++++
7	++++	6	0	++++
8	++++	6	0	0

* These rabbits received 0.5 cc. of filtrate A_s per kilogram of body weight.

† These rabbits received from 4 to 6 cc. of filtrate T_L 527 per kilogram of body weight.

‡ These rabbits received 0.2 cc. of filtrate A_s per kilogram of body weight.

NUMBER OF INJECTIONS NECESSARY TO RENDER PERITONEUM
IMMUNE TO *B. TYPHOSUS* CULTURE FILTRATE

Twelve rabbits, in each of which definite skin reactions had been obtained following the intraperitoneal injection of *B. typhosus* culture filtrate (A_s), were divided into three groups.

Group 1 (four rabbits): Each of these received two intraperitoneal doses of *B. typhosus* culture filtrate at three day intervals (T_L 527, 5 cc. per kilogram of body weight) and were then retested after three days with filtrate A_s, receiving 0.1 cc. of A_s intracutaneously, followed in twenty hours by 0.5 cc. per kilogram of body weight intraperitoneally. The four rabbits still showed hemorrhagic necrosis at the site of the skin injection, indicating that they had not been rendered immune to the intraperitoneal injections.

Group 2 (four rabbits): The experiments made on group 1 were repeated in all details, save for the fact that three peritoneal immunizing doses were given instead of two. On being retested, only two rabbits gave a positive reaction, while two gave negative reactions.

Group 3 (four rabbits): The experiments made on group 1 were repeated in all details except that four peritoneal immunizing injections were given at three day intervals. On being retested, two rabbits still gave a positive reaction, while two gave entirely negative responses.

It is thus evident that three intraperitoneal injections of *B. typhosus* culture filtrate may be sufficient to render the peritoneum immune to this filtrate. While three and four such injections each rendered 50 per cent of the rabbits immune, previous experiments have shown that five or more injections produced immunity in all of the rabbits so tested.

CONCLUSIONS AND SUMMARY

A modification of the phenomenon of local skin reactivity introduced by Schwartzman is described in this report. This modification consists in the employment of an intraperitoneal instead of an intravenous, injection of toxic substance twenty hours after such a preliminary inoculation into the skin.

By means of this modification, the principle of local peritoneal immunity was demonstrated. Rabbits in which the intraperitoneal injection of *B. typhosus* culture filtrate was able to elicit the Schwartzman phenomenon in previously prepared skin sites were rendered negative to this phenomenon by repeated injections of this culture filtrate intraperitoneally. It was then shown that this skin reaction could still be produced if the reacting factors were introduced intravenously. It must thus be concluded that the immunity produced under these circumstances was of a distinctly local character involving only the peritoneum, and that the entire organism was not yet immune.

It was also determined that between three and four injections of *B. typhosus* culture filtrate were necessary to render the peritoneum immune to this filtrate.

PERNICIOUS ANEMIA

BLOOD REGENERATION DURING EARLY REMISSION *

MATTHEW C. RIDDLE, M.D.

Fellow in Medicine of the National Research Council

PORTLAND, ORE.

The use of liver in pernicious anemia, following the discovery of its therapeutic value by Minot and Murphy,¹ has greatly increased the knowledge on the nature of blood regeneration during remission in this disease. The contributions to this subject of Peabody² and of Minot, Murphy, Cohn and their associates³ have been particularly valuable. According to their observations, the fundamental defect in hematopoiesis during a relapse in pernicious anemia depends on the inability of the primitive red blood cells of bone-marrow to differentiate normally to their adult state. As a result, the hematopoietic tissue of bone-marrow becomes hyperplastic and crowded with megaloblasts. The regenerative activity of bone-marrow being restricted in this fashion, the numbers of red blood cells in the peripheral blood decrease, and many of those present are abnormal. The liver,⁴ kidneys⁵ and stomach⁶ contain a substance which appears to stimulate the maturation of the primitive red blood cells and consequently have a therapeutic action in

* Submitted for publication, Feb. 1, 1930.

* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan, Ann Arbor.

1. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, *J. A. M. A.* **87**:470 (Aug. 14) 1926; A Diet Rich in Liver in the Treatment of Pernicious Anemia, *ibid.* **89**:759 (Sept. 3) 1927.

2. Peabody, F. W.: The Pathology of the Bone Marrow in Pernicious Anemia, *Am. J. Path.* **3**:179, 1927.

3. Minot, G. R.; Murphy, W. P., and Stetson, R. P.: Response of the Reticulocytes to Liver Therapy Particularly in Pernicious Anemia, *Am. J. M. Sc.* **175**:581, 1928. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract: Effects upon the Production of Immature and Mature Red Blood Cells, *Am. J. M. Sc.* **175**:599, 1928. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia, *J. Biol. Chem.* **77**:325, 1928.

4. Isaacs, R.; Sturgis, C. C., and Smith, M.: Treatment of Pernicious Anemia, *J. A. M. A.* **91**:1687 (Dec. 1) 1928. Minot et al. (footnotes 1 and 3).

5. McCann, W. S.: Effects of Kidney on Blood Regeneration in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **25**:255, 1928. Minot and Murphy (footnote 1).

6. Sturgis, C. C., and Isaacs, R.: Desiccated Stomach in the Treatment of Pernicious Anemia, *J. A. M. A.* **93**:747 (Sept. 7) 1929.

pernicious anemia. When these organs or active preparations of them are fed in sufficient quantity to patients with pernicious anemia, a remission is produced promptly and invariably, and a rapid regeneration of the blood takes place. The regeneration of blood under these circumstances proceeds in such a characteristic fashion that the sequence of events following liver therapy in a particular patient can be predicted with considerable accuracy when the important controlling factors are known.

The purpose in this paper is to discuss certain of these factors which influence the character of blood regeneration in patients with pernicious anemia during liver therapy and to study the manner in which they produce their effect.

THE RETICULOCYTE RESPONSE

In a practical sense, the appearance of increased numbers of reticulocytes in the blood during the first two or three weeks of liver medication, referred to as the reticulocyte response in this paper, is a very important phenomenon. It has some diagnostic significance as, with certain exceptions,⁷ a typical reticulocyte response rarely follows liver therapy in diseases other than pernicious anemia. It is of value in prognosis, since a well marked response signifies the onset of a satisfactory remission. Likewise, it may be used to measure the potency of preparations of unknown value and is at present the only reliable standard by which they may be assayed.⁸ The extent of the reticulocyte increase also provides a measure of the efficacy of treatment in any given case.

An increase in reticulocytes occurs as a rule only in patients in whom the concentration of erythrocytes in the peripheral blood is less than 3.5 million red blood cells per cubic millimeter of blood before treatment. In patients having more than 3.5 million red blood cells per cubic millimeter of blood, regeneration of blood takes place without an increase in the numbers of reticulocytes in the peripheral circulation.

The important features of the reticulocyte response are its magnitude and the rate at which it takes place. The rate and magnitude of the response are in a sense interdependent, since the numbers of reticulo-

7. Ashford, B. K.: Evaluation of Liver Extract Treatment in Treatment of Anemias of Sprue: Preliminary Note, *J. A. M. A.* **91**:242 (July 28) 1928. Isaacs, R.; Sturgis, C. C., and Smith, M.: Tapeworm Anemia: Therapeutic Observations, *Arch. Int. Med.* **42**:313 (Sept.) 1928. Vaughan, J.: Investigation of a Series of Cases of Secondary Anemia Treated with Liver or Liver Extract, *Lancet* **1**:1063, 1928. Dyke, S. C.: Liver Therapy in Secondary Anemia, *ibid.* **1**:1192, 1929. Minot et al. (footnote 3, first reference).

8. Minot et al. (footnote 3, second reference).

cytes present at any given time are necessarily smaller, other factors being equal, the more slowly the reticulocytes appear in the blood.

The magnitude of the reticulocyte response is most conveniently expressed either in terms of the concentration of reticulocytes in the blood when their numbers are greatest or as the maximum percentage of erythrocytes containing reticulum observed during the response. The rate of the response is judged from the duration of treatment required to produce the first increase in the reticulocytes in the blood, the maximum number or percentage of reticulocytes observed and the return of the reticulocytes to normal.

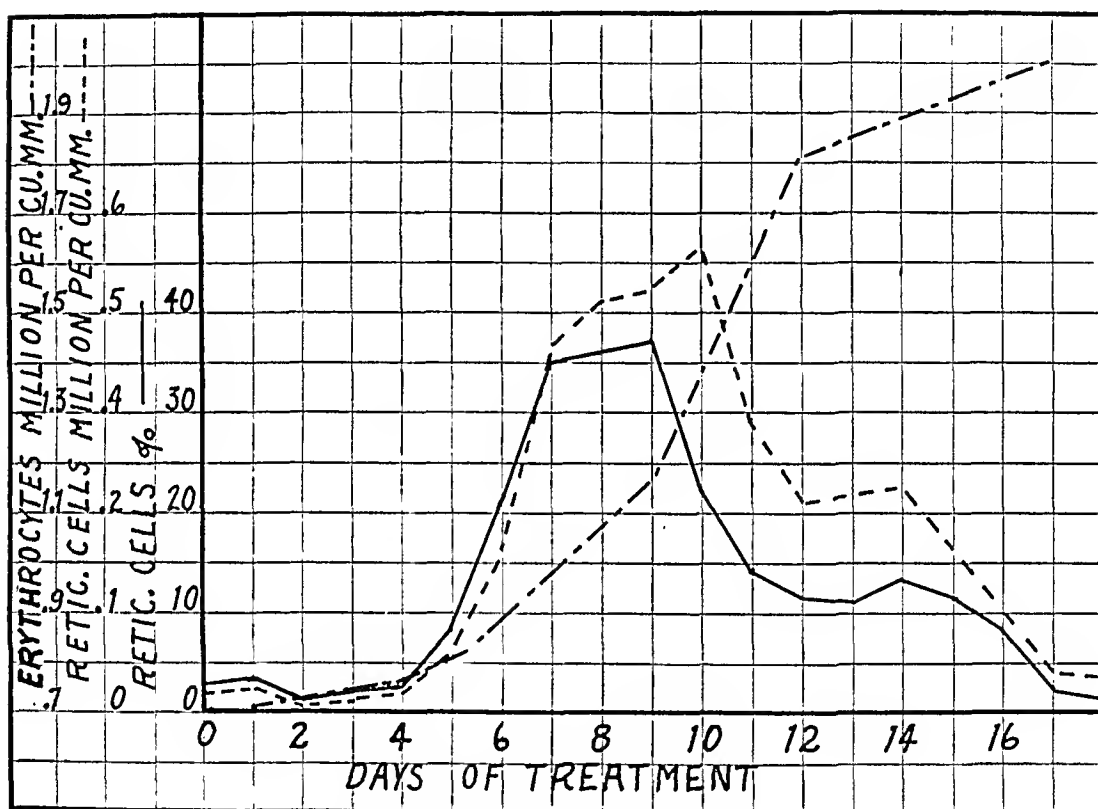


Chart 1.—The changes in the erythrocyte concentration, reticulocyte concentration and reticulocyte percentage in a patient with pernicious anemia during early remission. Treatment consisted of the contents of four vials of liver extract no. 343 (N.N.R.) daily.

When the daily values for the percentage or concentration of reticulocytes during adequate liver therapy are plotted graphically, the resulting curves usually resemble those shown in chart 1. These curves are asymmetrical, the rising slope of the curves representing the period of increasing values being shorter than the downward slope which represents the period of decreasing values, since, as will be shown later, the reticulocytes after being liberated from the bone-marrow probably remain as reticulocytes for a period of two days or more, and consequently tend to accumulate. Ordinarily, the percentage of reticulocytes

first increases above 2 between the second and fifth day of treatment, usually on the third day. A maximum percentage is found ordinarily between the fifth and eighth day. By the tenth to twentieth day of treatment the percentage of reticulocytes has usually fallen to a normal level. As in chart 1, maximum values often are seen on two or more consecutive days, and not infrequently a secondary rise in the percentage of the reticulocytes occurs during the latter part of the response.

The curve representing the actual concentration of reticulocytes is essentially similar to that of their percentage, but, owing to the increasing numbers of erythrocytes during the reticulocyte response, the peak of the curve occurs later than that of the percentage of the reticulocytes.

The form of the curves representing the reticulocyte response is a result of the interaction of the various factors which control the rate and magnitude of the response. To the accustomed eye, considerable information can be gained from an inspection of a characteristic curve as to the dosage of the active liver principle used, the presence of inhibiting factors such as chronic infection and the severity of the anemia before treatment. For example, high pointed curves, short in length, usually occur in patients with low blood counts fed large amounts of liver. Low, irregular, long curves usually indicate insufficient dosage of liver or the presence of inhibiting factors.

MAGNITUDE OF THE RETICULOCYTE RESPONSE

The extensive studies of Minot³ and his associates and of others⁹ have shown that the reticulocyte response in uncomplicated cases of pernicious anemia depends principally on the condition of the hematopoietic tissue in the bone-marrow and the amount of effective liver substance used in treatment. If adequate amounts of liver are used, the magnitude of the response is suggested by them to be directly proportional to the hyperplasia of the bone-marrow and inversely proportional to the concentration of erythrocytes in the blood before treatment. Minot and his associates¹⁰ were able to express mathematically this relationship between the red blood cell count and the magnitude of the response. Their equations representing this relationship are:

$$EpR = \frac{EoR}{1-R} = 0.73 - 0.2 Eo$$

Eo represents the red blood cell count before treatment, Ep the red blood cell count at the peak of the reticulocyte response and R the maximum percentage of reticulocytes observed during treatment. The

9. Sturgis, C. C.; Isaacs, R., and Smith, M.: The Treatment of Pernicious Anemia with a Liver Extract, *Ann. Int. Med.* **1**:983, 1928.

10. Minot et al. (footnote 3, second and third reference).

figures observed in patients under adequate treatment and those calculated by these formulas agree with reasonable accuracy. The equation $EpR = \frac{EoR}{1-R}$ ¹⁰ is based on the assumption that $EpR = Ep - Eo$ and that the increase in the value of E between o and p depends solely on the increment of reticulocytes. This idea is open to criticism as there is good evidence that new nonreticulated erythrocytes are produced and that effete erythrocytes are destroyed during this period. Cohn, Minot and their associates recognized this possibility, and in a discussion of this subject¹¹ stated:

These conditions can only be expected to obtain provided there has been no significant destruction of red blood cells, nor change in their concentration as a result of redistribution of body fluids. In fact not only must these same conditions obtain, but during the length of time that these three equations yield identical results there can have been no appreciable change of the reticulocytes to adult cells in the blood, nor delivery of adult forms from the bone marrow. In the majority of cases these quantities have not been identical, but their relations to each other are none the less significant.

These two processes must approximately counterbalance one another when the reticulocyte percentage is at its peak, as the equation $EpR = \frac{EoR}{1-R}$ agrees with the observed facts with reasonable accuracy. Evidence presented later in this paper indicates that this is true (chart 5).

Aside from their theoretical interest, these equations are of practical value and can be used as standards for determining the efficacy of treatment and the potency of preparations of unknown value.

Although, as Minot and his associates⁸ have suggested, in many respects it is more rational to consider the reticulocyte response in terms of the concentration of reticulocytes rather than their percentage, for the practical use of these formulas it is advantageous to express the relationship between the erythrocyte concentration before treatment and the magnitude of the reticulocyte response in terms of the maximum percentage of reticulocytes to avoid the necessity of making daily estimations of the erythrocyte concentration to obtain the value EpR . This may be accomplished by combining the two equations of Minot and Cohn, thus eliminating the value Ep .

$$EpR = \frac{EoR}{1-R} = 0.73 - 0.2 Eo$$

$$\frac{EoR}{1-R} = 0.73 - 0.2 Eo$$

$$R = \frac{0.73 - 0.2 Eo}{0.73 + 0.8 Eo}$$

The values of R thus calculated for various values of Eo are shown in table 1, and chart 2. In the chart there is close agreement between the curve representing the calculated values of R and the average

11. Minot et al. (footnote 3, third reference).

observed values of R in selected groups of patients with varying red blood cell counts before treatment, taken from the records of the Simpson Memorial Institute and those of Minot and Cohn and their associates.⁸ The figures used in making these average values are selected on the basis that those obtained from patients receiving amounts of liver inadequate to produce an effective response and those from patients in whom some inhibiting factor obviously prevented a typical response were not used in compiling these statistics.

In practice, when adequate treatment is given, the values for the maximum reticulocyte percentage actually observed and those calculated from this equation agree very well. Since the equation represents the average expected value of R, it is not surprising that individual varia-

TABLE 1.—*Expected Average Maximum Reticulocyte Percentage After Adequate Liver Treatment in Pernicious Anemia, with Various Red Blood Cell Counts**

Red Blood Cell Count in Millions per C.Mm. Before Treatment	Average Maximum Reticulocyte Percentage	Red Blood Cell Count in Millions per C.Mm. Before Treatment	Average Maximum Reticulocyte Percentage	Red Blood Cell Count in Millions per C.Mm. Before Treatment	Average Maximum Reticulocyte Percentage
...	1.3	26.5	2.6	7.5
0.1	87.7	1.4	24.3	2.7	6.6
0.2	77.5	1.5	22.3	2.8	5.7
0.3	69.1	1.6	20.4	2.9	4.9
0.4	61.9	1.7	18.7	3.0	4.1
0.5	55.7	1.8	17.1	3.1	3.4
0.6	50.4	1.9	15.6	3.2	2.7
0.7	45.7	2.0	14.1	3.3	2.1
0.8	41.6	2.1	12.9	3.4	1.5
0.9	38.0	2.2	11.6	3.5	0.9
1.0	34.6	2.3	10.5	3.6	0.3
1.1	31.7	2.4	9.4	3.65	0.0
1.2	29.0	2.5	8.4		

$$* \text{ Maximum reticulocyte percentage} = \frac{0.73 - 0.2 \text{ Eo}}{0.73 + 0.8 \text{ Eo}}$$

tions occur slightly above or below the expected values. Such variations may be attributed, in part at least, to the rhythmical daily variations of the reticulocyte percentage,¹² to mechanical difficulties in making extremely accurate estimations of the Eo or R or to individual variations in the condition of the bone-marrow of various patients with similar red blood cell counts.

Values distinctly under those expected from this equation usually indicate inadequate dosage of liver, the use of relatively impotent preparations or the presence of inhibiting factors.

The influence of the dosage of liver on the magnitude of the reticulocyte response has been thoroughly studied by Minot, Cohn and their

12. Porter, W. B., and Irving, H.: Reticulocytosis Produced by Liver Extract; Two, Three and Four Hour Interval Observations, Arch. Int. Med. 44:502 (Oct.) 1929. Riddle, M. C., and Sturgis, C. C.: The Effect of Massive Doses of Liver Extract on Patients with Pernicious Anemia, unpublished work.

$$R = \frac{0.73 - 0.2E_0}{0.73 + 0.8E_0}$$

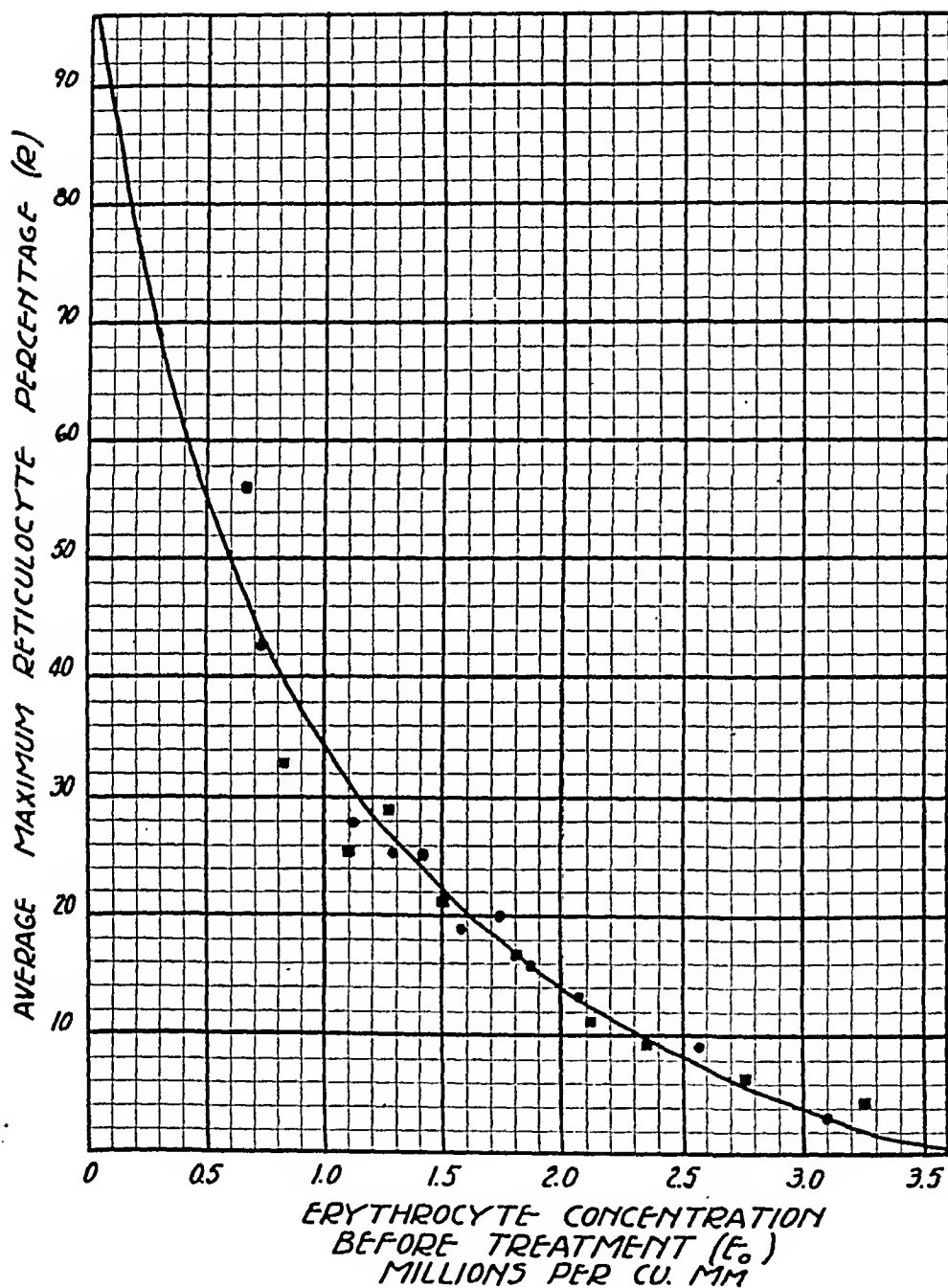


Chart 2.—The average maximum percentage of reticulocytes expected in patients with pernicious anemia after adequate liver extract therapy. The solid squares represent the average values of the maximum reticulocyte percentage observed in sixty-eight patients with pernicious anemia (author's cases) grouped according to the erythrocyte concentration before treatment. The solid circles represent similar values taken for eighty-nine patients observed by Minot and associates (footnote 3, second reference).

associates,³ who find that the minimum effective daily dose of liver is about 200 Gm. prepared weight. The use of 250 Gm. of liver daily or liver extract no. 343 ("New and Nonofficial Remedies") derived from 300 Gm. of liver usually produces a satisfactory response of the expected magnitude. Larger doses may not increase the magnitude of the response significantly, but when doses smaller than this are used daily, the magnitude of the response is less and is proportional to the dose used.⁸

THE RATE OF THE RETICULOCYTE RESPONSE

It is difficult to express the rate of the reticulocyte response quantitatively. Using the length of treatment necessary to produce a maximum percentage of reticulocytes as an index of the rate of the response, Minot and his associates⁸ found that the rate of the response is in a measure proportional to the dosage of liver extract.

TABLE 2.—*Number of Days of Adequate Liver Therapy Necessary to Produce the Beginning and Peak of Reticulocyte Response in Patients with Pernicious Anemia*

First Increase in Reticulocyte Percentage										
Number of days of treatment*.....	1	2	3	4	5					
Number of patients showing first increase in reticulocyte percentage.....	4	18	25	14	7					
Maximum Increase in Reticulocyte Percentage										
Number of days of treatment.....	4	5	6	7	8	9	10	11	12	13
Number of patients showing maximum percentages of reticulocytes.....	2	11	18	14	14	4	2	1	1	1

* The first day of treatment includes the first twenty-four hours after the initial dose of liver material is given, the second day of treatment the succeeding twenty-four hours, etc.

Table 2 shows the number of days of treatment required to produce the first increase and the maximum increase of the percentage of the reticulocytes in a group of sixty-eight patients with pernicious anemia receiving the contents of 3 vials of liver extract no. 343 (N. N. R.) derived from 300 Gm. of liver or more daily. Between one and five days of treatment was required to produce the first increase in reticulocyte percentage and from four to thirteen days the maximum percentage of reticulocytes in these patients. The first increase in the reticulocyte percentage usually was observed after from two to four days of treatment and the maximum reticulocyte percentage after from five to eight days of treatment.

When these same patients were classified according to the erythrocyte concentration present in the blood before treatment, as in tables 3 and 4, the level of the erythrocyte concentration did not appear to influence the time at which reticulocytes first appeared in increased per-

centage as, on the average, in each group this phenomenon occurred in approximately three days. The maximum reticulocyte percentage, however, appeared slightly earlier on the average the higher the initial erythrocyte concentration before treatment.

TABLE 3.—*Duration of Liver Treatment Required for First Increase of Reticulocyte Percentage**

Number of Patients	Erythrocyte Concentration Before Treatment, Millions per C.Mm.		Duration of Treatment Before First Increase in Reticulocytes, Days	
	Variation	Average	Variation	Average
11.....	0.5 - 1.0	0.83	2 - 4	3.4
23.....	1.0 - 1.5	1.25	1 - 5	2.8
14.....	1.5 - 2.0	1.80	2 - 5	3.2
15.....	2.0 - 2.5	2.22	1 - 5	3.1
5.....	2.5 - 3.5	3.15	2 - 4	3.2

* The dosage of liver medication varied with different patients but each received at least 300 Gm. of liver or an equivalent amount of liver extract daily.

TABLE 4.—*Duration of Liver Treatment Required for Maximum Increase of Reticulocyte Percentage**

Number of Patients	Erythrocyte Concentration Before Treatment, Millions per C.Mm.		Duration of Treatment Before Maximum of Reticulocytes, Days	
	Variation	Average	Variation	Average
11.....	0.5 - 1.0	0.83	4 - 10	7.5
23.....	1.0 - 1.5	1.25	4 - 13	7.2
14.....	1.5 - 2.0	1.80	5 - 9	7.0
15.....	2.0 - 2.5	2.22	5 - 11	6.7
5.....	2.5 - 3.5	3.5	5 - 8	6.6

* The dosage of liver medication varied with different patients but each received at least 300 Gm. of liver or an equivalent amount of liver extract daily.

TABLE 5.—*Relation of Liver Extract Dosage to Rate of Reticulocyte Response*

Number of Patients	First Increase of Reticulocyte Percentage, Days of Treatment		Maximum Increase of Reticulocyte Percentage, Days of Treatment		Liver Extract Dosage, Number of Vials*
	Variation	Average	Variation	Average	
8	5 - 9	6.5	7 - 12	8.9	Weak fractions of unknown potency
8	1 - 5	2.9	5 - 10	8.1	3 vials daily
8	2 - 4	3.0	4 - 8	6.4	4 vials daily
14	2 - 5	3.5	5 - 12	7.3	5 vials daily
21	1 - 5	2.8	5 - 13	7.0	6 vials daily
4	1 - 4	2.7	5 - 7	5.9	9 vials daily
5	2 - 3	2.2	5 - 6	5.2	15-30 vials (single dose)

* One vial of liver extract is derived from 100 Gm. of liver. With few exceptions liver extract no. 343 (N. N. R.) or equally effective preparations were used. In these exceptions, mostly confined to the group receiving 5 vials of liver extract daily, an earlier and less effective preparation of liver extract was used.

In table 5 sixty-eight patients receiving various amounts of liver extract, the dosage for each patient being uniform throughout the period of observation, were classified according to the dosage employed. The rate of the reticulocyte response as judged by the length of treatment necessary to produce the first increase and the maximum increase in the reticulocyte percentage, as a rule seemed to be accelerated by increasing dosages of liver extract. The only obvious exception occurs in the

group receiving liver extract derived from 500 Gm. of liver daily. The liver extract given to this group, in most cases, was not liver extract no. 343 (N. N. R.) but an earlier preparation which was definitely less effective. This may account for the retarded rate in this group. In the patients receiving weak extracts, the rate of the reticulocyte response was obviously delayed. In patients receiving extraordinarily large single doses of liver extract,¹³ the rate of the response was extremely rapid, two days being sufficient for the first increase in the reticulocyte response and five days for the maximum percentage values.

These figures indicate that the erythrocyte concentration in the blood of patients with pernicious anemia before treatment has little or no influence on the rate of the reticulocyte response. The rate of the response, however, appears to be accelerated in direct proportion, within certain limits, to the dosage of the effective liver principle employed.

THE RATE OF INCREASE OF THE ERYTHROCYTE CONCENTRATION DURING THE RETICULOCYTE RESPONSE

The foregoing discussion has been concerned with the general character, the magnitude and the rate of the reticulocyte response in large groups of patients. The following discussion has to do with a careful, analytic examination of data gathered from four critically studied patients.

These patients were given a single massive dose of liver extract.¹³ Determinations of the reticulocyte percentage were made every four hours, and determinations of the erythrocyte concentration every twelve hours furnished abundant material for mathematical analysis. In these patients an exceedingly rapid and typical reticulocyte response was produced beginning forty-eight hours after the administration of the liver extract, reaching a peak between the fourth and fifth day, and ending between the ninth and tenth day. When plotted graphically, the values of the erythrocyte concentration estimated at frequent intervals during the reticulocyte response usually form a symmetrical, sigmoid curve, as in chart 1, rather than a straight line. The increase in the erythrocyte concentration, at first slow, takes place at an increasingly rapid rate as the peak of the reticulocyte response is approached, then gradually becomes slower toward the end of the response.

The sigmoid character of this curve suggests that the general biologic law of growth and regeneration, represented by the equation $\log \frac{x}{a-x} = ka(t-t_1)$, described by Robertson,¹⁴ is applicable to the regeneration of blood during the reticulocyte response in patients with pernicious anemia.

13. Riddle and Sturgis (footnote 12, second reference).

14. Robertson, T. B.: *The Chemical Basis of Growth and Senescence*, Philadelphia, J. B. Lippincott Company, 1923.

In two of the four patients previously mentioned, the determinations of the erythrocyte concentration were sufficiently accurate for the successful application of this equation; in the remaining two, the data, while more variable than desirable, also seemed to follow this law.

As applied to the increase in the concentration of erythrocytes during the reticulocyte response, the value (x) in this equation represents the increase in the concentration of erythrocytes after any number days of treatment (t). The value (a) is a constant representing the total increase in the erythrocyte concentration during the reticulocyte response, and as blood regeneration takes place during the reticulocyte

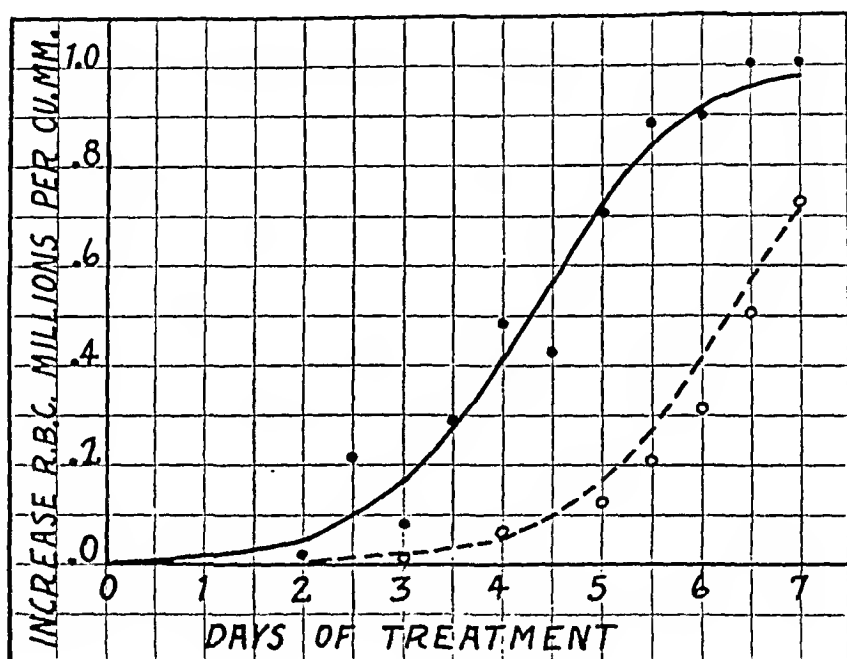


Chart 3.—The increase of the total erythrocyte concentration and of the concentration of nonreticulated erythrocytes in a patient with pernicious anemia after liver treatment. The solid line indicates the increase in the total erythrocyte concentration calculated from the equation $\log \frac{x}{1.02-x} = 0.54 t - 4.3$. The solid circles, the observed values of increase in the total erythrocyte concentration; the broken line, the increase in the concentration of nonreticulated erythrocytes calculated from the equation $\log \frac{x}{1.02-x} = 0.54 (t-6.3)$, and the open circles, the observed values of the concentration of nonreticulated erythrocytes obtained by subtracting the concentrations of the reticulocytes from the concentrations of erythrocytes.

response (x) approaches (a) as a limit. The value (t_1) represents the number of days of treatment when $x = \frac{a}{2}$, which usually is near the peak of the reticulocyte response. The value (k) is a constant which is determined for each different application of the formula. This application of Robertson's formula of growth and regeneration to the regen-

eration of blood during the reticulocyte response is illustrated in chart 3. In this patient the formula reads $\log \frac{x}{1.02-x} = 0.54$ ($t=4.3$). The concentration of erythrocytes in the blood was 0.69 million per cubic millimeter before treatment. At the end of the reticulocyte response, the erythrocyte concentration was 1.71 million per cubic millimeter. The difference between these two values or 1.02 is the value (a) in the equation. The value of (k) which best agreed with the data in this case was 0.53 so (ka) equals 0.54 in the equation. The peak of the reticulocyte response was observed to occur 104 hours or 4.3 days after the administration of liver giving the value for (t_1) as 4.3. In chart 3, the increase in erythrocyte concentration observed at twelve hour intervals and those calculated according to the formula appear to agree very satisfactorily considering the degree of accuracy with which red blood cells may be counted. In the same chart the increase in the numbers of nonreticulated erythrocytes, obtained by subtracting the observed concentration of reticulocytes from the observed concentration of erythrocytes, is compared with the values obtained from the equation $\log \frac{x}{1.02-x} = 0.54$ ($t=6.3$), which differs from the preceding equation only in the value for (t_1) which is in this case increased by two days to 6.3. The concentration of nonreticulated erythrocytes thus appears to increase in a manner similar to the total concentration of erythrocytes but later by approximately two days in this patient.

RATE OF LIBERATION OF THE RETICULOCYTES INTO THE BLOOD DURING THE RETICULOCYTE RESPONSE

Since reticulocytes are continually being liberated from the bone-marrow into the blood and while in the blood apparently are being transformed constantly into mature erythrocytes, no accurate estimate of the number released from the bone-marrow in a given time can be made unless the time required for the reticulocyte to lose its reticular material and become a mature erythrocyte is known.

A general idea of the rate of the liberation of reticulocytes into the blood can be obtained from the changes in their concentration in the blood from time to time. If the concentration is increasing it may be assumed that the rate of their release into the blood is greater than the rate of their transformation into mature erythrocytes and that they are accumulating in the blood. The reverse is true as their concentration decreases in the blood.

The data shown in chart 3 is evidence that in this patient the reticulocytes became nonreticulated after being approximately two days in the blood. With this knowledge and with the data on the reticulocyte concentration at frequent intervals, it was possible to apply Robertson's formula again. This time the value (x) represents the total number

of red blood cells liberated into the blood as reticulocytes, within a certain number of days of treatment (t) including both those still retaining reticulum and those transformed into mature erythrocytes. If the reticulocytes in this patient became mature in two days the concentration of reticulocytes at a given time (t), should equal the increase in the value of (x) between ($t-2$) and (t); in other words, the number of reticulocytes released during the preceding two days. When the various values of (x) for various values of (t) were obtained in this way from the observed values for the reticulocyte concentration, it was possible after a number of trials to find that the values for the constants (a)

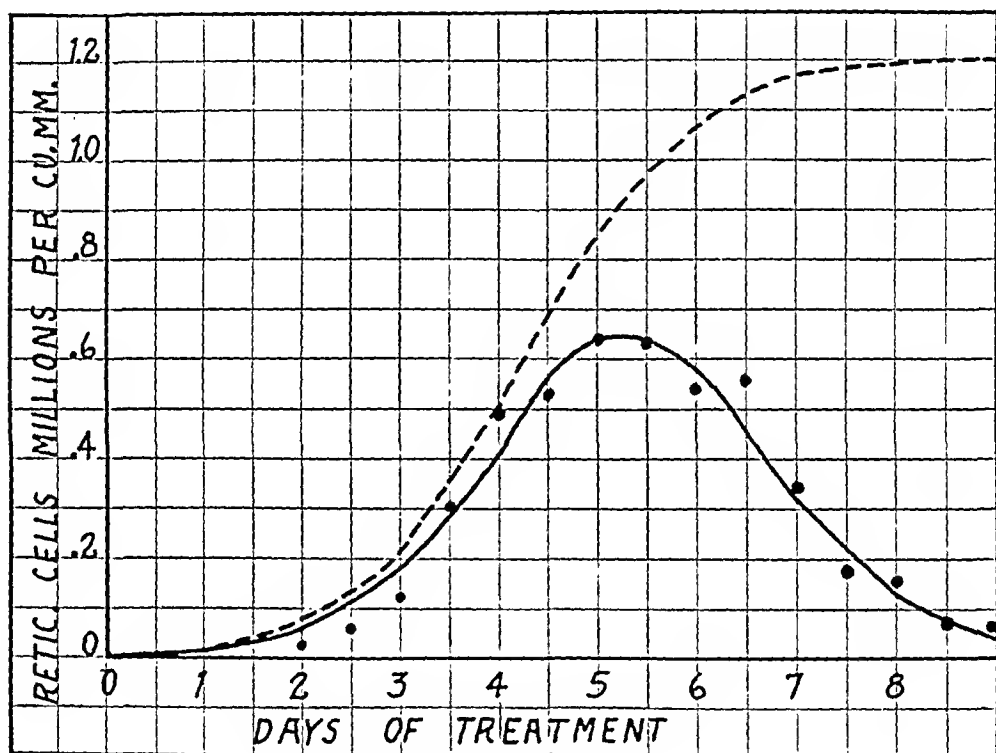


Chart 4.—The concentration of reticulocytes in a patient with pernicious anemia. The broken line indicates the values of the numbers of reticulocytes per cubic millimeter of blood liberated from the bone-marrow calculated from the equation $\log \frac{x}{1.2-x} = 0.54 (t-4.3)$; the solid line, the values of the concentration of reticulocytes after any number of days of treatment (t) obtained by subtracting values of x at $t-2$ from values of x at t ; the solid circles, the observed values of the concentration of reticulocytes.

and (k) which best satisfied the data at hand were 1.2 and 0.45, respectively. The value of t_1 from the previous use of the equation was known to be 4.3. Chart 4 presents the results obtained in this manner. The formula used is $\log \frac{x}{1.2-x} = 0.54 (t-4.3)$. The results calculated from this equation are plotted as a broken line. The curve drawn as a solid line represents the values of (x) at (t) minus the values of (x)

at $(t-2)$ and according to the reasoning employed should correspond to the curve of the reticulocyte concentration. The close agreement between the latter curve and the observed values for the concentration of the reticulocytes is obvious. This fact is further evidence that in this patient the reticulocytes lost their reticulum and became mature erythrocytes after being in the blood for two days. The value of (a) was 1.2 in this formula. In the formula for the increase in the erythrocyte concentration, the value of (a) was 1.02. This difference may be attributed to the destruction of effete red blood cells during the period involved. When the values of (x) representing the increase in the erythrocyte concentration obtained from the first equation $\log \frac{x}{1.02-x}$

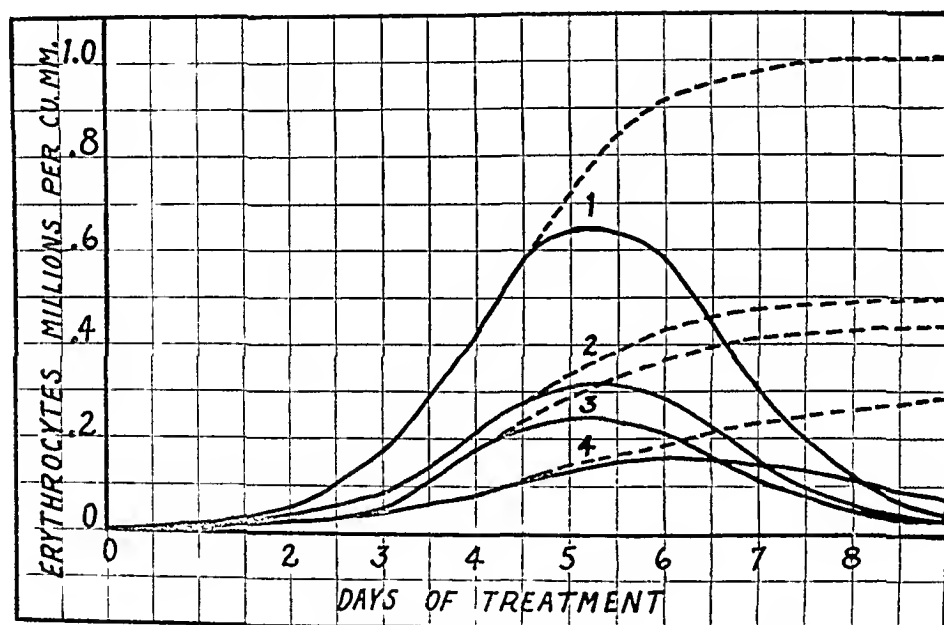


Chart 5.—The concentration of reticulocytes and the increase in concentration of erythrocytes during the reticulocyte response in four patients with pernicious anemia given a single massive dose of liver extract calculated from Robertson's equation for growth and regeneration. The solid lines indicate concentrations of reticulated erythrocytes which equal $(x_t - x_{t-2})$ in the following equations: patient 1, $\log \frac{x}{1.2-x} = 0.54$ ($t-4.3$); patient 2, $\log \frac{x}{0.6-x} = 0.50$ ($t-4.3$); patient 3, $\log \frac{x}{0.5-x} = 0.48$ ($t-4.3$); patient 4, $\log \frac{x}{0.45-x} = 0.3$ ($t-5.3$). The broken lines show the increase in total erythrocyte concentrations derived from the following equations; patient 1, $\log \frac{x}{1.02-x} = 0.54$ ($t-4.3$); patient 2, $\log \frac{x}{0.5-x} = 0.50$ ($t-4.3$); patient 3, $\log \frac{x}{0.43-x} = 0.48$ ($t-4.3$); patient 4, $\log \frac{x}{0.3-x} = 0.3$ ($t-5.2$).

The erythrocyte concentration in millions per cubic millimeter before treatment was as follows: patient 1, 0.69; patient 2, 1.43; patient 3, 1.87; patient 4, 2.82. The dosage of liver extract used in each case was as follows: patients 1, 2, 3, a single dose of the contents of thirty vials of liver extract; patient 4, a single dose of the contents of fifteen vials of liver extract.

$= 0.54$ ($t=4.3$) and the value of $x_t - x$ ($t=2$) from the equation $\log \frac{x}{1.2-x} = 0.54$ ($t=4.3$) representing the concentration of reticulocytes at t , between 0 and 4.3 days, are compared, they appear to be identical up to the peak of the reticulocyte response. This seems to indicate, as has been suggested before, that up to the peak of the response, the numbers of reticulocytes transformed into mature erythrocytes equals the numbers of effete erythrocytes destroyed and explains why the equation $EpR = \frac{EoR}{1-R}$ of Minot and his associates¹⁰ can be applied so satisfactorily.

Similar applications of Robertson's equation were made in the other three patients with similar results. In all of them the data indicated that the reticulocytes once liberated into the blood were transformed into mature erythrocytes in a two day period. Thus the rate of the reticulocyte response was the same, although the erythrocyte concentration before treatment varied in these four patients between 0.69 and 2.82. Chart 5 shows the curves representing the reticulocyte concentration and increase in the concentration of the erythrocytes calculated for these four patients in the manner already described and illustrates the point made previously that at the peak of the response the increase in the reticulocyte concentration equals the increase in the erythrocyte concentration.

Without further confirmation, this method of analysis cannot be said to have wide application. However, it offers a new method for approaching the solution of problems concerned with blood regeneration otherwise difficult of solution. Furthermore, it suggests that, under the circumstances, blood regeneration in these patients can be described by the formula of growth and regeneration used by Robertson.¹⁴

DIFFERENTIATION OF RETICULOCYTES IN THE BLOOD

In the patients previously discussed, under the intense stimulation of a very large dose of liver extract blood regeneration was unusually rapid, the entire reticulocyte response requiring less than ten days for its completion, a shorter period than ordinarily is required when smaller daily doses of the liver principle are used. It is probable that the transformation of the reticulocytes to mature erythrocytes, which in this case required only two days, requires longer in patients in whom the stimulus to blood regeneration is less intense. On the other hand, it also is likely that in normal persons and in persons less anemic than these patients the reticulocytes are retained in the bone-marrow for a longer time and are developed to a stage approaching nearer to maturity before their liberation and may consequently require less time in the blood to lose their reticulum. This matter appears to require special consideration in each individual case, as so many variable factors are involved.

In this discussion it has been assumed, and the evidence strongly favors the assumption, that once released into the blood reticulocytes develop into mature erythrocytes. As an alternative, it might be suggested that this does not necessarily occur, the reticulocytes being destroyed as such in the blood. The correlation between the numbers of reticulocytes appearing in the blood and the increase in the numbers of red blood cells during the reticulocyte response is so close that the destruction of significant numbers of reticulocytes seems improbable.

Furthermore, the changes in the microscopic appearance of the reticulocytes from day to day during the reticulocyte response indicates that while in the blood the reticulocyte gradually loses the substance which stains as reticular material. The reticulocyte population in any blood is not homogeneous. During periods of active blood regeneration, all gradations between normoblasts with heavy reticulation and mature erythrocytes may be found in a single drop of blood. The heaviest reticular material usually is seen in cells in which fragments of the normoblast nucleus are present. When only small strands of reticular material are present, the cell is indistinguishable from normal erythrocytes, except for the presence of the reticular material. From this evidence it appears that the reticular substance appears in large quantities as the normoblast loses its nucleus and that as the reticulocyte becomes increasingly mature the reticular substance is gradually lost, a mature erythrocyte being formed. This relationship between the degree of maturity of the red blood cell and its content of reticular material has been noted by various investigators.¹⁵

Characteristically, during the first few days of the reticulocyte response as these cells are rapidly increasing, the majority of the reticulocytes are heavily laden with reticular material. As the percentage of reticulocytes declines toward the end of the response, reticulocytes containing but little reticular material predominate. In other words, heavy reticulation is more frequent when the number of reticulocytes being released into the blood each day exceeds the number which have been present in the blood for a longer time. When the reverse is true, faintly reticulated cells are more frequent. This fact is shown in table 6 in which the reticulocytes are classified according to the amount of reticular material they contain. From the mathematical data presented, it was possible to compare the percentages of reticulocytes in this patient present each day which had been released into the blood between

15. Seyfarth, O., and Jurgens, R.: Untersuchungen über das Verhalten der vitalgranulierten roten Blutzellen (Retikulocyten) bei Embryonen und Neugeborenen, *Virchows Arch. f. path. Anat.* **266**:676, 1927. Davidson, S.: McCrie, J. G., and Gulland, G. L.: The Treatment of Pernicious Anemia with Liver and Liver Extracts, *Lancet* **1**:847, 1928. Schilling, V.: Wirkungen und Ausblicke der Lebertherapie bei Anaemia Perniciosa, *Klin. Wchnschr.* **1**:882, 1928.

twenty-four and forty-eight hours before with the degree of reticulation. From this comparison, it was deduced that reticulocytes with moderate to heavy reticulation had been liberated into the blood during the preceding twenty-four hours, those with faint reticulation having been present in the blood between twenty-four and forty-eight hours (table 6).

A mathematical analysis also was performed in the manner previously outlined in two patients who received daily the contents of three and four vials of liver extract no. 343 (N.N.R.), respectively. In the first patient the duration of the reticulocyte response, from the start of treatment until the end of the response, was twenty-four days. In this patient, during the first part of the reticulocyte response, according to the data, four days was required for the transformation of the

TABLE 6.—*Density of Reticular Substance in Reticulocytes in Relation to Age of Reticulocyte*

Days of Treatment	Percentage of Erythrocytes Containing Reticular Substance	Percentage of Reticulocytes in the Blood with Various Densities of Reticular Substance (Observed) *				Percentage of Reticulocytes Released into the Blood Between 24 and 48 Hours Before (Estimated)†
		++++	+++	++	+	
2	2.5	20	34	26	20	22
3	16.1	22	22	28	28	25
4	42.2	12	21	35	32	31
5	45.4	4	17	36	43	44
6	27.6	4	11	24	61	61
7	20.0	1	4	21	74	72
8	11.7	0	5	19	76	75
9	4.7	4	5	12	79	76

* +++++ = very dense reticular substance practically filling the reticulocyte; +++ = dense reticular substance in form of band, wreath or plaque; ++ = scattered clumps of reticular substance present; + = scattered strands of reticular substance.

† Estimated from the equation $\log \frac{x}{1.2-x} = .54 (t-4.3)$ (see chart 4).

reticulocytes in the blood into mature erythrocytes and during the latter part of the response three days was required. In the second patient the time required to complete the reticulocyte response was eighteen days, and for the disappearance of reticular material from the reticulocytes in the blood, three days. In these two patients in whom the reticulocyte response covered a longer period of time than in the patients previously discussed, the time required for the maturation of the reticulocytes in the blood into mature erythrocytes was proportionately longer. The rate of the maturation of the reticulocytes in the blood seemed to be related to the dosage of liver extract used.

Pepper,¹⁶ studying blood in vitro at body temperature, observed that the reticulation of reticulocytes began to decrease perceptibly after

16. Pepper, O. H. P.: Vitally Stainable Reticulation and Chromatic Granules in Erythrocytes in Vitro. Arch. Int. Med. 30:801 (Dec.) 1922.

eighteen hours and disappeared completely after seventy-two hours, a fact of interest in the present discussion.

In the blood of normal persons the reticulocytes contain only small amounts of reticular substance as a rule. If the observation that a lessened amount of reticular material is a sign of approaching maturity is sound, this would suggest that during the normal regeneration of blood the reticulocytes lose most of their reticular material before they are released from the bone-marrow, and that once present in the blood stream they lose the small amount of reticular material remaining within a relatively short time.

PHYSIOLOGIC CHANGES ACCOMPANYING BLOOD REGENERATION DURING REMISSION

The rapid regeneration of blood during the early part of remissions induced by the active principle contained in liver, recent investigations have shown, is accompanied by certain important physiologic changes in the blood and excreta. The amount of bilirubin in the blood, characteristically increased during relapse in pernicious anemia, rapidly decreases to a normal or subnormal level with the onset of remission.¹⁷ Iron, although used in large quantities for the manufacture of hemoglobin, is excreted in amounts greatly in excess of the iron intake during early remission.¹⁸ It is well known that an iron deficiency is not present during relapse, that iron is stored in considerable quantities in the body despite the anemia, and that iron therapy is illogical in pernicious anemia. During the early part of remission, the blood sugar during fasting becomes lowered,¹⁹ the restoration of appetite possibly being related to the relative hypoglycemia thus produced. Endogenous uric acid is manufactured and excreted in large quantities during the period of the reticulocyte response.²⁰ The amount of endogenous uric acid excreted in excess of the normal excretion is proportional to the increase in the numbers of red blood cells in the blood. From the figures given in table 7, it appears that on the average with the increase of a million red blood cells per cubic millimeter of blood approximately 10 Gm. of endogenous uric acid is excreted in the urine. The destruction of normoblast nuclei appears to be the source of this endogenous uric acid, and

17. Murphy, W. P.; Monroe, R. T., and Fitz, R.: Changes in the Composition of Blood in Pernicious Anemia, *J. A. M. A.* **88**:1211 (April 16) 1927.

18. Riecker, H. H., and Winters, M. E.: Serum Iron Studies, *Proc. Am. Soc. Clin. Investigation*, *J. Clin. Investigation* **7**:497, 1929.

19. Riddle, M. C.: The Blood Sugar During Remission in Pernicious Anemia, unpublished work. Blotner, H., and Murphy, W. P.: The Effect of Liver on the Blood Sugar Level, *J. A. M. A.* **92**:1332 (April 20) 1929.

20. Riddle, M. C., and Sturgis, C. C.: The Endogenous Uric Acid Metabolism in Pernicious Anemia, *Proc. Am. Soc. Clin. Investigation*, *J. Clin. Investigation* **7**:498, 1929. Riddle, M. C.: The Endogenous Uric Acid Metabolism in Pernicious Anemia, *J. Clin. Investigation* **8**:69, 1929.

it seems likely that the uric acid of endogenous origin normally excreted in the urine is derived principally from this source. This idea has confirmation in the researches of Krafka ²¹ on the excretion of endogenous uric acid in the Dalmation coach-hound during blood regeneration after hemorrhage and the observations of Isaacs ²² on the uric acid metabolism in polycythemia.

The endogenous uric acid metabolism, being so intimately related to blood regeneration, is a reasonably reliable biochemical index of blood production during early remission. The rise in the concentration of uric acid of endogenous origin in the blood and its excretion in increased amounts in the urine apparently have the same significance as the increase in the numbers of reticulocytes in the blood, and can be detected earlier, as changes in the endogenous uric acid metabolism usually

TABLE 7.—*Relation of Endogenous Uric Acid Excretion to the Increase in the Erythrocyte Concentration During Remission in Pernicious Anemia*

Patient	Days of Treatment	Endogenous Uric Acid Excretion, Gm.	Increase in Erythrocyte Concentration Million per C. Mm.	Uric Acid Excretion per Million Increase in Erythrocyte Concentration, Gm.
1	8	5.60	0.74	7.6
2	21	20.15	2.39	8.5
3	42	33.59	3.66	9.2
4	14	10.09	1.09	9.3
5	14	10.15	1.04	9.8
6	19	19.73	1.95	10.1
7	12	7.44	0.71	10.5
8	9	8.80	0.79	11.2
9	14	10.71	0.95	11.3
10	8	4.90	0.43	11.4

precede similar changes in the reticulocyte concentration in the blood by one or two days. According to Muller and his associates,²³ there is also an increase in the cholesterol and lecithin content of the blood plasma which accompanies the reticulocyte response during early remission.

COMMENT

According to the evidence presented in this paper, the conclusion may be drawn, in agreement with the observations of Minot and his associates,²⁴ that aside from the presence of inhibiting complications in patients with pernicious anemia, the two principal factors that regulate the reticulocyte response to liver therapy are the condition of the hema-

21. Krafka, J.: Endogenous Uric Acid and Hematopoiesis, *J. Biol. Chem.* **83**:409, 1929.

22. Isaacs, R.: Pathologic Physiology of Polycythemia Vera, *Arch. Int. Med.* **31**:289 (Feb.) 1923.

23. Muller, G. L.; Castle, W. B.; Goode, E., and Rose, M.: Relation of Cholesterol and Lecithin to Remission in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **25**:567, 1927-1928.

24. Minot et al. (footnote 3, first and second references).

topoietic tissue of the bone-marrow before treatment and the amount of the active principle contained in liver used in treatment.

The concentration of erythrocytes in a patient's blood before treatment, being inversely proportional to the degree of bone-marrow hyperplasia, is a satisfactory index of the extent of the hyperplasia and consequently can be used in mathematical formulas by which the average magnitude of the reticulocyte response to adequate liver medication in patients can be predicted with reasonable accuracy. The condition of the bone-marrow before treatment apparently does not influence directly the rate of differentiation of the primitive red blood-forming cells of bone-marrow to their more mature erythrocyte form after liver is administered. The reticulocyte response, figures show, occurs approximately at the same rate in patients with varying degrees of anemia when similar doses of liver or liver extract are used. Indirectly, the condition of the bone-marrow before treatment may modify the velocity of the reticulocyte response, as the data at hand suggest that the rate of the release of blood cells from the hematopoietic tissue of bone-marrow into the blood is proportioned both to the rate at which they are differentiating and to the numbers released into the blood in unit periods of time. The dosage of liver or liver extract used appears to influence directly the rate of cellular differentiation in the hematopoietic tissue of bone-marrow, and consequently influences in a direct manner the rate at which reticulocytes are liberated into the blood and the rate of the reticulocyte response. The magnitude of the reticulocyte response, being principally determined by the numbers of primitive red blood-forming cells in the bone-marrow available for transformation into reticulocytes and for their liberation from the bone-marrow into the blood, is influenced only in an indirect manner by the dosage of liver principle employed. The numbers of reticulocytes that accumulate in the blood at the peak of the response depend on the numbers formed in bone-marrow and released into the blood and the length of time reticulocytes remain as such in the blood. The magnitude of the response thus depends indirectly on the rate at which the reticulocytes are formed from the more immature cells of the bone-marrow. This effect is modified to a certain extent by the probability that if the rate of differentiation of the primitive red blood cells of bone-marrow into reticulocytes is slow, the differentiation of reticulocytes into erythrocytes in the blood also will be slow, and they will therefore tend to accumulate in greater numbers in the blood.

According to these theoretical considerations of the influence of the condition of the bone-marrow and the dosage of the liver principle on the rate, magnitude and character of the reticulocyte response, the rate and magnitude of the response are to a certain extent interdependent

and modify one another in the complex regenerative processes associated with blood formation during early remission after liver therapy in pernicious anemia.

The general law of biologic growth and regeneration widely applied by Robertson¹⁴ to various problems of growth and regeneration in plants and animals appears to be applicable to the phenomenon of the reticulocyte response. It should be emphasized that the application of this formula can be attempted only when the data are accurate and abundant and the reticulocyte response is typical and uniform. The use of this formula when it can be applied offers a new method for the solution of problems concerned with blood regeneration otherwise difficult of solution.

With the aid of this formula, an estimate was made of the length of time required for the reticulocytes in the blood of four patients given a massive dose of liver extract to become differentiated to their mature erythrocyte form. In these patients, blood regeneration took place at an unusually rapid rate as a result of the use of an extremely large amount of liver extract. The reticulocytes seemed to reach maturity and become indistinguishable from other erythrocytes two days after their liberation from the bone-marrow. In two other patients who received daily the contents of three and four vials of liver extract, respectively, the reticulocyte response developed at a slower rate, the differentiation of erythrocytes from reticulocytes in the blood requiring from three to four days.

The relations noted between the amount and density of reticular substance and the degree of maturity of the reticulocytes supports the evidence, derived from Robertson's formula, that the reticulocytes in the blood of the four patients given a massive dose of liver extract required two days in the blood stream for differentiation into mature cells. This evidence corroborates what has been noted by others,¹⁵ namely, that a large amount of reticular substance in a reticulocyte is a sign of relative immaturity of the red blood cells and that a scanty amount of this material is a sign of approaching maturity. Early in the response to liver therapy, as the reticulocytes increase, a greater proportion of them contain more reticular material than after the peak of the response has been reached, which indicates that early in the response the reticulocytes are liberated from the bone-marrow in a more immature form than later, that is, near the end of the response. Also, the proportion of reticulocytes with a small amount of reticular substance becomes greater as the reticulocyte response proceeds. A comparison of the degree of reticulation with the daily changes in the concentrations of reticulocytes and mature erythrocytes indicated that the reticulocytes containing heavy reticular material present at any given time had appeared in the blood

during the previous twenty-four hours. The faintly reticulated reticulocytes seemed to disappear within the succeeding twenty-four hours as they became mature in these four patients in whom the reticulocyte response was unusually rapid. When the length of time that the reticulocytes persisted as such in the blood was known, it was also possible with Robertson's equation to reproduce accurately in mathematical terms the curves representing the concentration of reticulocytes.

SUMMARY

1. From evidence collected from a group of sixty-eight patients with pernicious anemia undergoing remission as a result of liver treatment and from a consideration of the theoretical factors that influence blood regeneration under these circumstances, it appears that the magnitude of the reticulocyte response is governed directly by the extent of the bone-marrow hyperplasia during relapse, and that the rate of the reticulocyte response is governed directly by the dosage of the active principle contained in liver.

2. As the magnitude and the rate of the reticulocyte response are to a certain extent interdependent, the condition of the bone-marrow apparently influences indirectly the rate of the response, and the dosage of liver used influences indirectly the magnitude of the response.

3. The percentage of reticulocytes expected, on the average, at the peak of the reticulocyte response can be formulated in terms of the concentration of erythrocytes before treatment. The equation $R = \frac{0.73 - 0.2 E_0}{0.73 + 0.8 E_0}$ which represents this relationship can be used in determining the efficiency of treatment and in testing the potency of extracts of unknown value.

4. For four patients whose collected data were satisfactory for mathematical analysis, the blood regeneration was formulated according to an equation used by Robertson to express a general law of biologic growth and regeneration.

5. When the rate at which the reticulocytes in the blood of these patients were transformed into mature erythrocytes was estimated by this equation, the curve representing the concentration of reticulocytes during the reticulocyte response could be duplicated mathematically.

6. It was estimated that in these patients two days were required for the differentiation of reticulocytes in the blood into mature erythrocytes. In two other patients in whom the stimulus to regeneration of blood was less intense, it was estimated that between three and four days were required for the maturation of reticulocytes in the blood to their mature form.

7. A correlation of the relative maturity of the reticulocyte with the amount of reticular material it contained showed that, under the circumstances present, reticulocytes containing small amounts of reticular material disappeared during the following day.

8. When the amount of reticular substance in a reticulocyte was used as a standard for estimating its degree of maturity, it was found that during the early part of the reticulocyte response reticulocytes were liberated in an earlier stage of development than toward the end of the response.

9. The rate at which reticulocytes are liberated from the bone-marrow into the blood appears to be a factor of importance which influences the rate and magnitude and velocity of the reticulocyte response. The rate of the liberation of the reticulocytes into the blood seems to be proportional to the rate at which they are formed from the more primitive red blood cells within the bone-marrow and to the numbers of reticulocytes being formed there.

10. An increase of a million red blood cells per cubic millimeter of blood is accompanied by an excretion of approximately 10 Gm. of endogenous uric acid in patients with pernicious anemia during early remission.

RED BLOOD CELL SIZE IN ANEMIA

ITS VALUE IN DIFFERENTIAL DIAGNOSIS *

WILLIAM P. MURPHY, M.D.

AND

GREENE FITZHUGH, M.D.

BOSTON

A knowledge of the relative size of the red blood cells may be of definite value in differentiating between the types of anemia. This information may be obtained by a careful study of the red blood cells in a stained smear made from the patient's blood. Determinations of the mean diameter of the red blood cells by actual measurement of a number of cells, as suggested by Price-Jones,¹ or by a modification of this method, have been made use of frequently; but this method is rather too time-consuming to be used extensively. Pijper² and others have suggested a diffraction method for determining the size of the red blood cells. Haden³ suggested the determination of the volume of the average red blood cell by means of a simple calculation based on a knowledge of the red blood cell count and the total percentage volume of cells as determined by means of the hematocrit. Jorgensen and Warburg⁴ have reviewed much of the literature with reference to the size of the red blood cells in its relation to the anemias, so that a detailed discussion of this subject is not given here.

The observations here recorded were made with the idea of further determining the value of the average individual cell volume in a more or less routine study of a group of persons with normal blood and in a rather large group showing anemia. In some instances, measurements were made also of the mean diameter of the red blood cells.

* Submitted for publication, Dec. 18, 1929.

* From the Medical Wards of the Peter Bent Brigham Hospital.

* This study was aided by a grant from the Proctor Fund of the Harvard University Medical School for the study of chronic disease.

1. Price-Jones, C.: The Variation in the Sizes of the Red Blood Cells, *Brit. M. J.* **2**:1418, 1910.

2. Pijper, A.: An Improved Diffraction Method for Diagnosing and Following the Course of Pernicious and Other Anemias, *Brit. M. J.* **1**:635, 1929.

3. Haden, R. L.: Accurate Criteria for Differentiating Anemias, *Arch. Int. Med.* **31**:766 (May) 1923.

4. Jorgensen, S., and Warburg, E. J.: The Indices and Diameters of the Erythrocytes and the Best Haematological Criterion of Pernicious Anemia: I. Historical Notes and Normal Values, *Acta med. Scandinav.* **66**:109, 1926.

PROCEDURE

The procedure followed in these cases was essentially the same in each instance. With a dry syringe and needle, 10 cc. of blood was withdrawn from an arm vein and placed in a test tube previously prepared by evaporating to dryness 2 cc. of a 1.6 per cent solution of sodium oxalate as described by Keith, Rowntree and Geraghty⁵ and by Murphy, Monroe and Fitz.⁶ After the solution was mixed thoroughly by gently inverting the tube several times, standardized red blood cell-counting pipets were filled so that the red blood cells might be counted later. A determination of the hemoglobin by the Sahli method as modified by Osgood and Haskins⁷ was made in many instances, although the determinations made by comparison with Tallqvist or Dare scales were used occasionally. Smears of the blood were made also so that the diameter of the red blood cells might be measured. In each instance 250 red blood cells were measured in stained smears of blood as described by Bell, Thomas and Means.⁸ The oxalated blood was then centrifugated in a straight, thick-walled test tube at high speed (approximately 2,900 revolutions per minute) for one-half hour, and the percentage volume of the cells and plasma was determined after measuring the columns of each.

The average individual cell volume may be determined by dividing the percentage volume of red blood cells as determined by the hematocrit by the number of red blood cells in 100 cc. of oxalated venous blood. The figure is recorded in cubic centimeters times ten to the minus eleventh power. This calculation may be carried out according to the following simple formula in which 42 is the percentage volume of red blood cells as determined by the hematocrit and there are 5,000,000 red blood cells per cubic millimeter:

$$\frac{\text{Per cent of cells by hematocrit}}{\text{Number of R.B.C. in 100 cc. blood}} = \frac{42}{5,000,000 \times 1,000 \times 100} = 8.4 \times 10^{-11} \text{ cc.}$$

The cases so studied have been divided for convenience of discussion in the text into several groups. The observations recorded in each group are shown in the corresponding tables.

RED BLOOD CELLS IN NORMAL GROUP

Normal Persons.—Thirty-two determinations were made on thirty-one essentially normal persons, male and female, the ages varying from 20 to 70 years. In this group the average red blood cell count is 5,100,000 cells per cubic millimeter. The average percentage volume of red blood cells as determined by means of the hematocrit is 42.9. The average calculated individual cell volume is 8.42×10^{-11} cc.

5. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16**:547 (Oct.) 1915.

6. Murphy, W. P.; Monroe, R. T., and Fitz, R.: Changes in Composition of Blood in Pernicious Anemia: Treated by a Diet Rich in Liver, *J. A. M. A.* **88**:1211 (April 16) 1927.

7. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* **57**:107, 1923.

8. Bell, J. R.; Thomas, F. K., and Means, J. H.: Studies on Red Blood Cell Diameter: I. In Health and in Pernicious Anemia, *J. Clin. Investigation* **3**:229, 1926.

Normal Blood.—This group is made up of twenty-nine persons in whom no essential variation from normal could be demonstrated in the hemoglobin or red blood cell count in spite of the fact that they could not be considered well. Thirty-one determinations were made in this group. The average red blood cell count is 4,900,000 per cubic millimeter of blood. The average percentage volume of red blood cells is 40.8, whereas the average individual cell volume is 8.32×10^{-11} cc.

It may be seen from an analysis of tables 1 and 1A that the normal individual cell volume generally varies between 8×10^{-11} and 9×10^{-11}

TABLE 1.—*Observations on Normal Persons*

Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hematocrit, per Cent of Cells	Hemoglobin in Grams per 100 Cc.
1.....	9.1	4.94	45	13.76
2.....	9.0	4.80	43	15.04
3.....	9.0	4.79	43	13.76
4.....	8.9	5.30	47	13.76
5.....	8.9	5.28	47	14.50
6.....	8.9	4.92	44	13.76
7.....	8.7	4.58	40	11.73
8.....	8.6	4.87	42	12.14
9.....	8.6	4.78	41	13.76
10.....	8.6	5.14	44	14.62
11.....	8.6	4.99	43	12.55
12.....	8.6	5.24	45	13.76
13.....	8.5	4.83	41	14.62
14.....	8.5	4.85	41	13.76
15.....	8.5	5.19	44	13.52
16.....	8.5	5.54	47	12.90
17.....	8.4	5.00	42	13.76
18.....	8.4	4.88	41	14.62
19.....	8.3	4.60	38	12.01
20.....	8.3	5.19	43	14.62
21.....	8.3	5.51	46	13.22
22.....	8.2	5.45	45	15.59
23.....	8.2	4.75	39	11.59
24.....	8.1	4.93	40	11.04
25.....	8.1	5.56	46	14.90
26.....	8.1	5.21	42	12.29
27.....	8.0	5.74	46	13.76
28.....	8.0	5.62	45	13.76
29.....	8.0	5.37	43	14.50
29.....	7.9	5.30	42	13.76
30.....	7.9	4.84	38	11.19
31.....	7.8	5.11	40	13.22
Average.....	8.42	5.10	42.9	13.49

cc., although a small number, especially in the latter group, have an individual cell volume either greater than 9 or less than 8.

Haden's ³ average individual cell volume figure lies even above the upper limit considered as normal in this series. This is no doubt the result of two variations in our figures. Haden recorded an average red blood cell count which is lower than the one here recorded. On the other hand, the hematocrit percentage total cell volume figures recorded here are lower than those recorded by Haden, which suggests that the packing of the cells was greater in this series. Haden has suggested this possible variation, which is to be expected. The packing will vary according to the speed and duration of the centrifugation. In order to

make the individual cell volume figure useful, it will be necessary for each laboratory to establish a normal figure after centrifugating a small series of normal bloods. If the method is to be used infrequently it would be possible to centrifugate each time a tube of normal blood with the blood to be tested and use the normal individual cell volume figure so obtained as a control.

The percentage total red blood cell volume as determined by the hematocrit compares favorably with recent previously reported results,

TABLE 1A.—*Observations on Normal Blood*

Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hemato-crit, per Cent of Cells	Hemo-globin in Grams per 100 Cc.	Diagnosis
1	9.4	5.00	47	15.48	Adenomatous goiter with hyperthyroidism
2	9.1	5.04	46	13.76	Cardiorenal disease
3	9.1	4.62	42	13.76	Hypertension; myocarditis
4	9.0	4.98	45	13.76	Myocarditis; slight uterine hemorrhage
5	8.9	4.70	42	12.28	Osteo-arthritis, chronic
6	8.9	4.61	41	13.76	Nutritional disturbance
7	8.9	4.60	41	12.90	Osteo-arthritis; mild hypothyroidism
8	8.8	4.67	41	12.14	Nutritional disturbance
9	8.8	4.30	38	11.73	Endometrial polyp
10	8.7	5.15	45	13.76	Sprue
11	8.7	4.95	43	14.35	Asthmatic bronchitis
12	8.7	4.62	40	13.11	Infectious jaundice, acute
12	8.5	4.47	38	12.00	Infectious jaundice, acute
13	8.6	4.64	40	12.90	Bronchopneumonia; asthma
14	8.4	4.62	39	12.90	Fibroid of uterus
15	8.4	4.40	37	13.76	Infectious jaundice, chronic
16	8.3	4.44	37	11.60	Question of duodenal ulcer
17	8.2	5.00	46	12.28	Infectious jaundice, acute
18	8.2	4.87	40	12.90	Nutritional disturbance
19	8.2	4.90	40	13.25	Duodenal ulcer; hypertension
19	8.0	4.50	36	11.88	Duodenal ulcer; hypertension
20	8.0	4.51	36	11.73	Hodgkin's disease
21	7.7	5.22	40	12.90	Nutritional disturbance
22	7.7	5.48	42	15.48	Mild hypothyroidism
23	7.7	4.95	38	11.73	Ulcerated colitis
24	7.7	4.73	36	12.15	Lacerated cervix; menopause
25	7.7	4.93	38	11.88	Intestinal indigestion
26	7.7	4.92	38	13.11	Obesity
27	7.6	5.82	44	12.97	Duodenal ulcer
28	7.4	6.05	45	12.83	Infarct of heart; coronary occlusion
29	7.1	5.90	42	13.93	Diabetes mellitus; jaundice
Average	8.32	4.90	40.8	13.00	

notably by Osgood,⁹ Osgood and Haskins,¹⁰ Jorgensen and Warburg⁴ and Haden.³

Ponder¹¹ and others have determined the red blood cell volume from certain measurements of the cell. Harting¹² estimated the average

9. Osgood, E. E.: Hemoglobin, Color Index, Saturation Index and Volume Index Standards in Men, Arch. Int. Med. **37**:685 (May) 1926.

10. Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, Arch. Int. Med. **39**:643 (May) 1927.

11. Ponder, E.: The Erythrocyte and the Action of Simple Hemolysins, Edinburgh, Oliver & Boyd, 1924.

12. Harting: Das Mikroskop, Theorie, Gebrauch, Geschichte und gegenwärtiger Zustand desselben, Braunschweig, 1859, p. 950.

volume as 76 cubic microns. Welcker¹³ obtained the figure of 72 cubic microns, whereas Ponder¹¹ has considered the average to be between 70 and 80 cubic microns. If the average individual cell volume figure 8.4×10^{-11} cc. obtained by us be changed to cubic microns, 84 cubic microns would represent the average normal red blood cell volume here observed. It is possible that this figure is slightly too high because, owing to the shape of the red blood cells, complete packing by means of the hematocrit method may not be possible.

RED BLOOD CELLS IN VARIOUS TYPES OF ANEMIA

Pernicious Anemia.—One hundred and thirty-two determinations were made on 106 patients with a diagnosis of pernicious anemia. The individual cell volume in the majority of instances was 10×10^{-11} cc. or greater. In general, this figure varied inversely with the red blood cell count, the lower figures being found in those cases with a more nearly normal count, and especially after treatment with liver or liver extract. In only a few of these cases was the red blood cell count definitely within normal limits, and very few determinations are recorded in this group, where patients had been treated with liver over a long period of time. Observations made on the blood of patients treated for longer periods of time and with a red blood cell count essentially normal are discussed in another paragraph. In a few of the cases studied complications were present. Only four cases (101, 102, 103, 104) recorded in table 2 need be discussed from this standpoint. In case 101 the patient had been treated with liver for about two years, during which time his red blood cell count was normal. He was then admitted to the hospital with an acute respiratory infection and acute nephritis, at which time this determination was made. Complete recovery occurred, and under liver treatment the patient has remained well for a year. Myxedema developed to complicate the picture in case 102. With thyroid extract and liver treatment, it has been possible for the patient to maintain a fair state of health, but with a red blood cell count generally somewhat below normal. The diagnosis in case 103 has been somewhat questionable. This patient is a negress who entered the hospital with a marked anemia. Sick cells could not be demonstrated; free hydrochloric acid was absent from the gastric contents studied by the fractional test method for two hours after an Ewald test meal. Under treatment with liver, a reticulocyte rise occurred, followed by the usual red blood cell rise, and the patient has remained essentially well with similar treatment since. In case 104, the patient was started on liver treatment approximately two years before the recorded deter-

13. Welcker, H.: Grösse, Zahl, Volum Oberfläche und Farbe der Blutkörperchen bei Menschen und bei Thieren, Ztschr. f. rat. Med. **20**:257, 1864.

TABLE 2.—*Observations in Pernicious Anemia*

Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hemato- crit, per Cent of Cells	Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hemato- crit, per Cent of Cells
1	17.6	0.91	16	48	11.8	1.69	20
2	17.4	0.57	10	49	11.8	2.46	48
3	16.8	1.01	17	49	10.7*	4.29	46
4	16.8	1.19	20	50	11.8	4.05	48
5	16.5	1.09	18	51	11.7	1.80	21
6	15.8	2.21	35	52	11.6	2.14	25
7	15.6	0.90	14	53	11.6	2.84	33
8	15.3	1.24	19	54	11.5	2.35	27
9	15.3	1.18	18	55	11.5	3.40	39
9	10.3*	2.42	25	56	11.4	1.40	16
9	9.4*	3.31	31	57	11.4	2.37	27
10	15.2	0.66	10	58	11.3	2.12	24
11	15.1	1.98	30	59	11.3*	3.38	38
11	11.6*	3.20	37	59	10.7*	3.56	38
12	14.8	1.35	20	59	8.6*	4.08	36
13	14.5	1.93	28	60	11.2	0.98	11
14	14.5	2.00	29	61	11.2	1.60	18
15	14.4	3.06	44	62	11.0	1.64	18
16	14.1	1.98	28	63	11.0	1.90	21
17	14.0	0.93	13	64	11.0	2.90	32
18	14.0	1.00	14	65	11.0	3.18	35
19	13.8	1.67	23	66	11.0	3.38	37
20	13.6*	1.99	27	67	10.9	3.13	34
20	10.5*	2.37	25	68	10.9*	3.30	36
20	13.3*	1.88	25	69	10.8*	5.20	56
20	13.1*	1.98	26	70	10.7*	3.94	42
21	13.5	1.70	23	71	10.7*	4.20	45
22	13.5	1.70	23	72	10.6	1.42	15
22	10.9*	3.20	35	72	9.7*	3.08	30
23	13.5	3.19	43	73	10.6	1.79	19
23	11.6	2.52	29	74	10.6	2.07	22
24	13.3	1.05	14	75	10.6	2.73	29
25	13.3	1.35	18	76	10.6	3.30	35
26	13.1	1.53	20	76	10.4	3.56	37
26	10.2*	4.00	41	77	10.5*	4.10	43
27	13.1	4.20	55	78	10.4	2.30	24
28	13.0	2.74	36	79	10.4*	3.76	39
28	10.0*	3.90	39	80	10.4*	4.24	44
29	13.0	3.15	41	81	10.3	2.13	22
29	9.1*	4.18	38	82	10.3	2.90	30
30	12.8	1.80	23	83	10.2	3.51	36
30	9.4	1.70	16	84	10.2*	4.00	41
30	11.6	1.64	19	85	10.2*	4.12	42
30	11.4	1.74	20	86	10.1	3.44	35
30	14.0	1.78	25	87	10.1*	3.45	35
31	12.8*	3.10	40	88	10.1	3.97	40
32	12.7	1.10	14	89	10.0	1.40	14
32	12.6	1.03	13	90	10.0	1.50	15
33	12.7	1.18	15	90	9.7*	1.45	14
34	12.7	1.42	18	90	9.9*	3.63	35
35	12.7	2.60	33	91	10.0	1.80	18
36	12.7	2.76	35	92	10.0	3.10	31
37	12.7	3.30	42	93	10.0*	3.50	35
38	12.4	2.90	36	94	10.0*	4.70	47
38	9.0*	4.24	38	95	9.8*	4.50	44
39	12.3	2.20	27	96	9.7*	3.30	32
39	10.5*	2.76	29	97	9.6*	3.98	38
40	12.3	3.00	37	98	9.1*	4.29	39
41	12.3	3.64	45	99	9.1*	4.50	41
42	12.2	1.64	20	100	8.9*	3.84	34
43	11.9	1.51	18	101	8.9*	4.50	40
44	11.9	1.60	19	102	8.8*	3.54	31
44	13.0	1.69	22	103	8.1	1.60	13
45	11.8	1.02	12	104	7.4	3.53	26
46	11.8	1.10	13	105	7.4	3.90	29
47	11.8	1.52	18	106	6.9	4.66	32

* Some liver was ingested before observation was made.

minations were made. At that time the history, symptoms, physical signs and blood examination were all typical of pernicious anemia with changes resulting from an early combined degeneration of the spinal cord. At the time of the observation here recorded there was a drop in the blood count; occult blood was demonstrated in the feces, and there was evidence of progression of the cord changes. Roentgen examination of the stomach showed a lesion, probably carcinoma. Exploratory operation was refused. The diagnosis of pernicious anemia, although recorded, is questionable in cases 105 and 106. In each instance no free hydrochloric acid was found in the gastric contents. The color index, smear examination and history, however, suggest a secondary type of anemia. Hemorrhage from the intestinal tract was demonstrated quite certainly in case 105, although roentgenologic examination failed to demonstrate a pathologic condition.

Questionable Pernicious Anemia.—Five other cases with high individual cell volume figures recorded in table 2A might properly be discussed at this point. The first three cases are placed in this group because it was impossible to make a positive diagnosis of pernicious anemia, although certain features of the cases were suggestive of this disease. In each instance free hydrochloric acid was absent from the gastric contents, and the blood picture would fit in satisfactorily for this diagnosis, although there were certain atypical symptoms. In case 2, the patient was admitted with symptoms suggesting disease of the gall-bladder, but cholecystographic studies failed to show such a disturbance. In case 3, there was a basal metabolic rate of +36 per cent and an atypical anemia. The diagnosis was recorded in the hospital record as chronic alcoholism, Korsakoff's syndrome. Case 4¹⁴ showed an absence of free hydrochloric acid in the gastric contents and definite macrocytosis in the blood smear. There was, however, occult blood in the feces, and roentgenologic studies showed a large mass in the stomach. Liver extract was given, followed by a rise in the reticulocyte count and in the red blood cell count. An exploratory operation revealed an adenocarcinoma involving a large part of the posterior wall of the stomach. Although a part of the anemia was the result of loss of blood, it is quite likely that pernicious anemia was also present. The diagnosis must remain somewhat in doubt in case 5 also. This patient had a moderate degree of anemia, not typical of that found with pernicious anemia and a small amount of free hydrochloric acid was found in the gastric contents. Symptoms were present, however, suggesting rather extensive disturbance in the central nervous system, not entirely typical

14. This patient was observed through the courtesy of Dr. J. P. O'Hare and Dr. John Homans of the Peter Bent Brigham Hospital staff.

of those found in combined systemic disease involving the posterior and lateral columns of the cord. A moderate increase in the red blood cell count resulted from treatment with liver. A diagnosis of multiple sclerosis was made.

Anemia Due to Chronic Loss of Blood.—The record of individual cell volume determinations in fifty-two patients having anemia resulting from chronic loss of blood are recorded in table 3. In the majority of these cases many determinations were made; but in each instance the first determination is recorded only when the anemia was most marked. The individual cell volume figure for this group of cases varies from the very low one of 5.2×10^{-11} cc. to the average normal figure of 8.5×10^{-11} cc. Only about 20 per cent of the figures fall within the range which is considered normal. In no case here recorded was the figure higher than normal, which was found in the cases of pernicious

TABLE 2A.—Observations in Questionable Pernicious Anemia

Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hematoerit, per Cent of Cells
1.....	9.9	2.72	27
1.....	10.5	2.68	28
2.....	11.6	3.10	36
2.....	11.0	3.17	35
2.....	10.6	3.57	38
3.....	10.9	3.57	39
4.....	11.5	1.83	21
4.....	10.5	2.10	22
5.....	10.0	4.10	41

anemia. It is interesting to note, however, that during improvement of the blood condition under the influence of treatment the individual cell volume, when low at first, gradually increased to a normal figure. Figures illustrating this point are shown in table 3A (case 3 of table 3). The cause of the loss of blood appears not to have been a factor in determining the size of the cells. Likewise, there seems to be no definite relation between the cell volume and the red blood cell or hemoglobin level before treatment was started.

Anemia Due to Acute Loss of Blood.—In table 4 are recorded twenty-eight observations made in twelve patients having hemorrhage either just prior to or during the period of observation. In these patients the average individual cell volume was greater than the normal cell volume in most instances shortly following the hemorrhage. The observations recorded in cases 1 and 4 show well the gradual change to normal or even smaller than normal individual cell volume during improvement in the blood. No special treatment was given in these two cases to enhance blood formation. In case 12, bleeding occurred

TABLE 3.—*Observations in Anemia Due to Chronic Loss of Blood*

Case	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemato-erit, per Cent of Cells	Hemo-globin in Grams per 100 Ce.	Source of Hemorrhage
1	5.2	4.80	25	6.88	Cancer of ascending colon
2	5.3	5.10	27	6.62	Uterine hemorrhage
3	5.6	4.85	27	5.94	Uterine hemorrhage
4	5.6	3.76	22	5.50	Uterine hemorrhage
5	5.7	4.00	23	4.14	Hemorrhoids
6	5.8	4.80	28	8.55	Uterine hemorrhage
7	6.0	2.17	13	2.34	Uterine hemorrhage
8	6.1	5.40	33	8.00	Uterine hemorrhage
9	6.2	3.57	22	4.28	Uterine hemorrhage
10	6.2	3.40	21	4.83	Uterine hemorrhage
11	6.3	4.30	27	10.03	Intestinal hemorrhage
12	6.3	5.10	32	7.17	Uterine hemorrhage
13	6.4	4.71	30	7.58	Uterine hemorrhage
14	6.6	4.09	27	6.62	Uterine hemorrhage
15	6.6	3.97	26	7.17	Uterine hemorrhage
16	6.7	4.60	31	7.58	Uterine hemorrhage
17	6.7	2.97	20	3.45	Hemorrhoids
18	6.8	3.10	21	7.74	Cancer of stomach
19	6.8	3.38	23	4.55	Uterine hemorrhage
20	6.8	4.71	32	9.65	Intestinal hemorrhage
21	6.9	2.17	15	6.88	Cancer of stomach
22	6.9	2.75	19	5.16	Cancer of stomach
23	7.0	3.72	26	6.02	Cancer of stomach
24	7.1	3.40	24	4.96	Uterine hemorrhage
25	7.1	2.97	21	3.17	Hemorrhoids
26	7.2	2.35	17	2.07	Cancer of intestine
27	7.2	4.06	29	5.79	Uterine hemorrhage
28	7.2	4.74	34	8.70	Uterine hemorrhage
29	7.3	4.55	33	11.19	Uterine hemorrhage
30	7.4	1.85	14	4.14	Uterine hemorrhage
31	7.4	2.73	20	5.52	Uterine hemorrhage
32	7.5	3.20	24	6.88	Hemorrhoids
33	7.5	4.30	32	10.03	Uterine hemorrhage
34	7.5	3.10	23	6.21	Uterine hemorrhage
35	7.5	4.69	35	10.03	Uterine hemorrhage
36	7.6	3.02	23	4.97	Uterine hemorrhage
37	7.6	3.82	29	6.06	Uterine hemorrhage
38	7.7	3.14	24	4.42	Uterine hemorrhage
39	7.7	3.49	27	5.38	Uterine hemorrhage
40	7.8	2.70	21	4.42	Uterine hemorrhage
41	7.8	3.00	23	3.31	Uterine hemorrhage
42	7.9	2.80	22	6.88	Cancer of stomach
43	7.9	3.30	26	7.31	Uterine hemorrhage
44	8.1	4.31	35	9.80	Uterine hemorrhage
45	8.2	3.66	30	8.28	Uterine hemorrhage
46	8.2	3.68	30	8.55	Hemorrhoids
47	8.3	1.80	15	3.45	Hemorrhoids
48	8.3	2.64	22	4.68	Intestinal hemorrhage
49	8.3	3.00	25	6.21	Hemorrhoids
50	8.4	2.75	23	4.14	Cancer of stomach
51	8.5	2.71	23	8.60	Hemorrhoids
52	8.5	3.64	31	8.60	Hemorrhoids

TABLE 3A.—*Increase in Individual Cell Volume (Case 3, Table 3)*

Date of Test	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemato-erit, per Cent of Cells	Hemoglobin in Grams per 100 Ce.
11/13/28.....	5.6	4.85	27	5.94
11/19/28.....	6.3	4.27	27	5.52
11/26/28.....	5.9	4.77	28	6.06
12/ 2/29.....	5.4	4.97	27	5.79
12/12/28.....	5.3	4.89	26	6.48
12/19/28.....	5.7	4.54	26	5.94
12/26/28.....	5.2	4.99	26	6.06
1/ 7/29.....	6.5	4.90	32	6.48
1/14/29.....	7.1	5.19	37	9.10
1/23/29.....	8.2	4.87	40	10.08
2/13/29.....	8.6	5.24	45	12.99

frequently during the period of observation, which no doubt explains the rather constantly increased cell volume. Cases of this series would hardly be confused clinically with cases of pernicious anemia as the presence of hemorrhage was very obvious.

"Secondary" Anemia Not Caused by Hemorrhage.—In a group of twenty-four patients having a secondary anemia from some cause other than hemorrhage, the cell volume varied considerably, about one-third being below normal, whereas a smaller group showed greater than

TABLE 4.—*Observations in Anemia Due to Acute Loss of Blood*

Case	Date of Test	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemato-erit, per Cent of Cells	Hemo-globin in Grams per 100 Ce.	Source of Hemorrhage
1	10/ 1	11.3	2.17	25	6.75	Gastric ulcer
1	10/11	9.3	2.70	25	5.80	
1	10/19	8.6	3.00	26	6.48	
1	12/ 2	7.0	4.70	33	7.86	
2	10.5	2.10	22	6.21	Postoperative
3	1/12	10.1	2.68	27	8.14	Gastric ulcer
3	2/ 2	8.0	3.23	26	12.05	
4	10/21	10.1	1.97	20	4.42	Gastric ulcer
4	10/27	8.7	2.88	25	5.80	
4	11/ 5	8.2	3.55	29	6.75	
4	11/11	8.4	3.70	31	6.75	
4	11/18	7.5	4.54	34	9.38	
4	12/ 2	6.5	4.76	31	8.41	
4	12/16	7.3	5.10	37	10.05	
5	9.9	2.71	27	7.17	Uterine hemorrhage
6	9.9	3.14	31	8.70	Uterine hemorrhage
7	9.8	2.76	27	6.75	Uterine hemorrhage
8	9.3	3.54	33	11.03	Hemorrhoids
9	9.2	1.74	16	2.90	Uterine hemorrhage
10	8.7	2.87	25	6.75	Gastric ulcer
11	7.4	3.36	25	7.59	Gastric ulcer
12	1/ 5	7.4	2.16	16	4.14	Hemorrhoids; epistaxis
12	1/18	11.7	2.40	28	6.35	
12	1/26	9.7	2.90	23	7.17	
12	2/ 3	9.9	3.13	31	9.52	
12	2/10	10.2	3.53	36	9.90	
12	2/17	9.5	3.88	37	11.60	
12	2/24	9.3	4.09	38	11.47	

normal volume. The anemia in some of these cases was probably either of the chronic chlorotic type or to be explained on the basis of nutritional disturbances. In these cases the diagnosis is recorded as "undetermined." With the exception of the last patient, the individual cell volume is definitely smaller than that usually found during relapse in patients with pernicious anemia. The cause for the anemia in this last case was undetermined. The patient's mother had pernicious anemia, but the patient herself had free hydrochloric acid in the gastric contents and no symptoms suggestive of this disease.

Pregnancy with Anemia.—The individual cell volume was studied in six patients having an anemia during pregnancy or following delivery.

TABLE 5.—*Observations in "Secondary" Anemia Not Caused by Hemorrhage*

Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hemato-crit, per Cent of Cells	Hemo-globin in Grams per 100 Cc.	Diagnosis
1	6.5	3.98	26	6.88	Nutritional disease
1	9.8	4.50	44	13.40	(After treatment with liver)
2	6.7	3.76	25	5.94	Diaphragmatic hernia
2	7.7	5.31	41	12.55	(After treatment with liver)
3	6.9	4.05	28	8.60	Nutritional disease
4	7.0	5.72	40	10.03	Chronic chlorosis
5	7.2	4.16	30	10.01	Erythema nodosum
6	7.5	4.69	25	10.03	Chronic chlorosis
7	7.5	4.65	35	8.60	Chronic chlorosis
8	7.9	4.55	36	9.37	Myxedema
9	7.9	4.21	33	10.05	Meningioma
10	8.1	2.46	20	7.74	Salpingitis; chronic oophoritis
11	8.3	3.40	28	8.27	Subacute bacterial endocarditis
12	8.3	4.32	36	Cholecystitis; cholelithiasis
12	8.4	3.10	26	7.86	
13	8.3	4.21	35	11.04	Myocarditis
13	8.9	3.14	28	8.82	
14	8.4	4.67	39	11.19	Not determined
15	8.5	3.61	31	8.69	Lead poisoning, chronic
16	8.6	5.10	44	11.19	Osteo-arthritis
17	8.6	4.06	35	10.04	Question of methemoglobinemia (paroxysmal)
18	8.7	4.94	43	12.03	Arteriosclerosis
19	8.7	4.37	38	12.03	Mild hypothyroidism
20	8.7	2.65	23	6.20	Obesity; nutritional disease
21	8.7	1.83	16	2.34	Chronic myocarditis; cerebral arterio-sclerosis
22	8.8	4.32	38	12.03	Not determined
23	8.9	3.61	32	7.60	Duodenal ulcer; arteriosclerosis peripheral
24	8.9	3.92	35	10.03	Arthritis, infectious
24	9.2	4.68	43	12.90	(After treatment with liver)
24	8.0	4.25	34	9.90	(After treatment with liver)
25	9.0	5.02	45	11.19	Not determined
26	9.0	4.99	45	10.03	Chronic chlorosis
27	9.0	3.33	30	9.40	Myxedema
28	9.2	5.10	47	12.03	Not determined
29	9.3	3.78	35	10.05	Hemopneumothorax; massive collapse of lung
30	9.3	3.00	28	7.60	Carcinoma of head of pancreas; jaundice
31	9.3	4.28	40	12.03	Not determined
32	10.0	4.08	41	11.19	Not determined

TABLE 6.—*Observations in Pregnancy with Anemia*

Case	Individual Cell Volume ($\times 10^{-11}$ Cc.)	Red Blood Cells in Millions per C.Mm.	Hemato-crit, per Cent of Cells	Hemo-globin in Grams per 100 Cc.	Comment
1	11.5	1.22	14	2.48	Postpartum anemia
1	9.0	4.24	38	11.19	One year later free hydrochloric acid present
2	9.7	3.90	38	12.90	During pregnancy
3	8.9	3.40	30	8.96	During pregnancy
4	8.8	2.44	21	5.10	Postpartum anemia
4	8.3	4.20	35	10.01	
4	8.2	4.40	36	11.45	
4	9.2	4.43	41	11.45	
4	8.6	4.73	41	11.18	
4	7.4	5.40	40	11.45	
5	7.5	2.94	22	6.06	During pregnancy
5	6.8	4.42	30	8.00	
5	6.9	4.80	33	7.72	
5	7.1	4.80	34	8.42	
5	7.6	4.76	36	8.82	
5	8.0	4.90	39	10.06	
5	8.6	4.43	38	10.02	
5	8.5	4.73	40	11.04	
6	6.3	4.76	30	5.52	During pregnancy; no free hydrochloric acid present

As may be seen from table 6, the figure for the individual cell volume varied considerably. In cases 1 and 4, the anemia occurred acutely after delivery and was not due to hemorrhage. Whether or not slight anemia had occurred previously in these patients is not known. Free hydrochloric acid was found in the gastric contents of the first patient. Only one other patient (case 6) was tested in this manner, and no free hydrochloric acid was found in specimens obtained up to two hours following an Ewald test meal. The anemia in this patient and in the others of the group, excepting in cases 1 and 4, was observed during the course of pregnancy. In each patient of the series the blood picture in most respects was characteristic of the secondary type. Although the cell

TABLE 7.—*Observations in Nephritis*

Case (× 10 ⁻¹¹ Cc.)	Individual Cell Volume	Edema	Red Blood Cells in Millions per C.Mm.	Hemato-erit, per Cent of Cells	Hemo-globin in Grams per 100 Cc.	Diagnosis
1	8.2	..	3.42	28	7.86	Chronic nephritis without edema
2	10.0	++++	2.70	28	8.55	Chronic nephritis with edema
2	9.2	++++	3.36	31	8.42	
2	8.4	+++	3.65	31	9.24	
2	8.0	++	3.15	25	8.27	
2	7.8	+	3.30	26	8.00	
2	9.6	+	2.90	28	6.76	
2	8.7	+	3.31	29	8.00	
2	9.0	+	3.75	34	10.05	
3	9.1	++++	3.74	34	10.06	Chronic nephritis with edema
3	7.5	++	5.03	38	10.08	
3	8.2	+++	3.90	32	10.05	
3	8.4	++	3.80	32	10.02	
3	8.6	++	3.58	31	10.02	
3	7.0	+	3.85	27	10.02	
3	8.2	+	3.56	29	8.55	
3	10.0	+++	3.82	38	9.38	
3	8.6	++	3.60	31	8.96	
4	10.2	..	1.57	16	7.74	Chronic nephritis without edema
5	11.4	++++	4.38	49	12.90	Chronic nephritis with edema

volume was definitely above the normal range in two cases of this series (cases 1 and 2), it is not likely that any of them fall into the group of so-called pernicious anemia of pregnancy.

Anemia in Nephritis.—Data concerning five patients with nephritis are given in table 7. Here again the individual cell volume in several instances was greater than the upper normal figures. The reason for this is not easy to determine, although clinically there was no difficulty in distinguishing them from the pernicious anemia group. Liver therapy failed to increase the red blood cells. Three patients of the group had nephritis with edema and the cases may be classed as so-called nephrosis. The remaining two patients had nephritis without edema. In those patients with edema, the individual cell volume was apparently influenced by the presence or absence of the edema, usually being increased during the periods of increased fluid retention.

RED BLOOD CELLS IN ERYTHREMIA AND MISCELLANEOUS BLOOD DISEASES

Erythremia.—Five patients with erythremia were observed, and the results are shown in table 8. In these patients, the individual cell volume was within or below the normal range.

TABLE 8.—*Observations with Erythremia*

Case	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemato-crit, per Cent of Cells	Hemo-globin in Grams per 100 Ce.	Diagnosis
1	7.1	6.10	43	13.8	Erythremia; cerebral thrombosis
1	9.1	5.82	53	13.8	
2	7.2	8.19	59	16.44	Erythremia
3	7.4	6.06	45	17.20	Erythremia
4	8.0	8.90	71	17.27	Erythremia
4	9.5	7.30	69	15.05	
5	8.6	6.80	59	15.47	Erythremia; hypertension

TABLE 9.—*Observations in Miscellaneous Blood Diseases*

Case	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemato-crit, per Cent of Cells	Hemo-globin in Grams per 100 Ce.	White Blood Cells per C.Mm.	Diagnosis
1	15.2	1.95	30	6.06	3,500	Leukemia, aleukemie lymphoid
2	12.8	2.10	27	7.59	2,900	Leukemia, aleukemie lymphoid
3	11.6	1.81	21	5.11	2,700	Leukemia, aleukemie lymphoid
4	12.1	1.48	18	Malignant lymphoma; jaundice
5	11.6	1.80	21	5.25	20,000	Leukemia, ehronic myeloid
6	11.1	1.35	15	2.90	3,000	Purpura hemorrhagica, acute
7	11.1	1.35	15	2.34	10,000	Leukemia, aleukemie myeloid
8	11.1	1.26	14	2.07	8,600	Leukemia, aleukemie myeloid
9	10.2	1.95	20	4.84	11,000	Leukemia, aleukemie myeloid
10	10.0	1.70	17	5.16	41,000	Leukemia, ehronic lymphatie
11	10.0	1.60	16	5.16	21,500	Leukemia, ehronic myeloid
12	9.9	0.91	9	1.52	2,100	Atypical blood disease
13	9.7	1.86	18	7.74	Leukemia, aleukemie myeloid
14	9.5	2.73	26	7.18	2,700	Atypical blood disease
15	9.4	4.69	44	12.02	204,100	Leukemia, ehronic myeloid
15	8.1	4.69	38	12.02	204,100	Leukemia, ehronic myeloid
16	9.3	2.15	20	4.84	5,200	Leukemia, aleukemie myeloid
16	9.3	1.81	17	3.86	5,500	Leukemia, aleukemie myeloid
17	9.2	2.50	23	9.45	12,000	Atypical blood disease
18	8.9	4.90	44	5.25	190,000	Leukemia, ehronic myeloid
18	6.5	4.90	32	5.25	190,000	Leukemia, ehronic myeloid
19	8.0	2.50	20	4.14	90,000	Leukemia, ehronic myeloid
20	7.7	3.65	28	9.45	3,800	Leukemia, aleukemie myeloid
21	6.5	4.60	30	9.45	6,000	Splenomegaly

Miscellaneous Blood Diseases.—In table 9 are recorded observations on a group of patients having some form of essential blood disturbance other than pernicious anemia. In many of these cases, especially those of aleukemic leukemia, it was difficult to distinguish from pernicious anemia. The determination of the individual cell volume did not help in this differentiation. The table shows that the majority of the determinations fall within the range generally found during relapse in patients with pernicious anemia. In only two patients (cases 10 and 12) was it considered necessary to subtract the height of the white blood cell column

from the total cell column in determining the cell hematocrit figure, although it is possible that a somewhat lower individual cell volume would have been found in other cases if this had been done. Difficulties in diagnosis were slight in those cases having the higher white blood cell counts, although diagnosis was difficult in the cases having low white blood counts. It is in such cases as the latter that aid in diagnosis is desired, but differentiation is not possible by a determination of the individual cell volume. A noteworthy fact is that the individual cell volume was normal or less than normal in the patients with the more nearly normal red blood cell counts. Such a state of affairs did not occur in the patients with pernicious anemia with higher counts, even if liver had been ingested for short periods of time.

COMPARISON WITH MEASUREMENTS OF THE MEAN DIAMETER

Measurements of the average individual cell volume and of the mean cell diameter were made on the same sample of venous blood in a series of patients with pernicious anemia and in a group of patients with various diagnoses. The mean diameter of the red blood cells in normal persons has been found by Bell, Thomas and Means⁸ to vary from 7.4 to 8 microns and by Medearis and Minot¹⁵ from 7.25 to 7.75 microns. These figures compare favorably with those obtained by others and especially those collected from the literature by Jorgensen and Warburg⁴ and by Ponder.¹¹ The mean diameter rarely exceeds 7.8 microns and for the purposes of this paper 8 microns is considered the upper limit of normal. Twenty-seven determinations were made of both the individual cell volume and the mean diameter of the red blood cells of twenty-five patients with pernicious anemia, in whom treatment with liver had been carried out for only brief periods of time or not at all, or in whom the red blood cell count had dropped because an insufficient amount of liver had been taken. In two of the patients the observations were made on two separate specimens of blood. The data is presented for comparison in table 10. The cases have been arranged according to the size of the mean cell diameter. In the first five cases, the mean diameter was within the normal range. In none of these five patients was the individual cell volume normal. In fact, in only two cases of the entire series was the individual cell volume figure within the normal range, namely, case 18 (case 102, table 2) and case 20 (case 103, table 2). The mean diameter measurement in both of these cases was distinctly greater than normal. It is very likely that in case 18 the individual cell volume figure represents the condition of the blood more

15. Medearis, D. N., and Minot, G. R.: Studies on Red Blood Cell Diameter: II. In Pernicious Anemia, Before and During Marked Remission, and in Myelogenous Leukemia, *J. Clin. Investigation* 3:541, 1927.

nearly than the mean diameter figure, as this patient had developed signs and symptoms of myxedema with a basal metabolic rate of —29 per cent. A more detailed discussion of this case has been recorded under case 102 of table 2. Case 20 has been discussed previously as case 103

TABLE 10.—*Comparison of Mean Diameter with Individual Cell Volume in Pernicious Anemia*

Case	Mean Diameter, Microns	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemoglobin in Grams per 100 Ce.
1.....	7.59	10.5	4.09	11.88
2.....	7.80	11.8	1.52	5.79
3.....	7.90	11.7	1.79	8.77
4.....	7.94	13.8	1.67	8.60
5.....	7.99	11.8	1.69	7.45
6.....	8.01	11.0	2.90	11.20
7.....	8.02	16.8	1.05	11.18
8.....	8.07	9.9	2.72	7.86
9.....	8.13	12.7	1.42	4.97
9A*.....	8.75	10.6	3.59	11.30
10.....	8.15	11.3	2.03	4.83
11.....	8.17	11.0	3.18	10.35
12.....	8.19	15.6	0.90	5.16
13.....	8.22	16.1	1.02	7.74
13A†.....	8.46	10.0	1.80	5.24
14.....	8.24	10.2	3.51	10.49
15.....	8.33	15.8	2.21	8.00
16.....	8.39	11.8	1.01	3.45
17.....	8.46	12.7	1.15	3.04
18.....	8.48	8.8	3.54	11.60
19.....	8.65	11.9	1.60	6.02
20.....	8.75	7.9	4.03	9.88
21.....	8.80	14.8	1.35
22.....	8.86	12.7	3.31	11.02
23.....	8.93	12.8	3.12	9.65
24.....	8.94	11.9	2.94	6.21
25.....	9.10	10.2	2.54	8.83

* 9A one year later than determination no. 9.

† 13A two weeks later than determination no. 13.

TABLE 11.—*Comparison of Mean Diameter with Individual Cell Volume in Cases of Pernicious Anemia in Which Treatment Has Been Given*

Case	Mean Diameter, Microns	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions per C.Mm.	Hemato-erit, per Cent of Cells	Hemoglobin in Grams per 100 Ce.
1.....	7.49	8.4	4.98	42	12.98
2.....	7.60	8.2	4.91	40	11.30
3.....	7.70	8.7	5.51	48	13.90
4.....	7.70	8.7	4.92	43	12.29
5.....	7.90	8.7	4.59	40	12.29
6.....	7.98	8.9	4.50	40	11.02
6.....	8.70	9.0	4.90	44	12.84
7.....	8.10	8.4	5.23	44	12.84
8.....	8.10	9.3	4.50	42	11.02
9.....	8.30	9.1	4.52	41	12.14
10.....	8.30	9.1	4.96	45	13.25
11.....	8.50	9.4	4.98	47	13.10
12.....	8.60	9.2	4.22	39	11.31

of table 2. In this group of patients the individual cell volume figure gave more definite information concerning the state of the red blood cells than did the much more difficult and technical determination of the mean cell diameter.

Studies were made on twelve patients with pernicious anemia who had received satisfactory liver treatment for a year or more during which time their red blood cell count had remained at or above 4,500,000 per cubic millimeter except in the patient recorded in case 12. The count in this case had remained above this level up to the time the cell diameters were measured when it was 4,220,000 per cubic millimeter. In one patient observations were made on two occasions about seven months apart so that a total of thirteen observations are recorded. In six instances both the mean diameter and individual cell volume figures fell within the normal range, whereas in two others, although the individual cell volume was normal, the mean diameter was greater than normal. In no instance, however, was the individual cell volume higher than the upper limit reached in a few of the normal blood specimens as recorded in tables 1 and 1A.

The figures noted in table 11 suggest that under proper liver treatment the red blood cells in a patient with pernicious anemia may be maintained at an essentially normal volume with, in some instances, a slightly greater than normal mean cell diameter. These observations corroborate the figures reported by Bell, Thomas and Means⁸; Medearis and Minot,¹⁵ Persons,¹⁶ and Fitzhugh and Persons,¹⁷ obtained by measurement of the mean diameter of the red blood cells in a group of patients with pernicious anemia treated with liver.

In the third group of cases in which a comparison was made of the individual cell volume and the mean cell diameter, thirty observations were made on twenty-four patients and the data are given in table 12. A detailed discussion of the figures will not be undertaken, as the points of difference in the two determinations may be seen readily by inspection of the table. Mention is made, however, of some aspects of those cases in which marked difference between the two figures occur. In case 1 (also case 1 of table 6) the patient had severe, acute anemia following labor. Hemorrhage did not occur. One year later, the individual cell volume was 9×10^{-11} cc. when the red blood cell count was only slightly below normal and the patient apparently in good health. At this time free hydrochloric acid was found in the gastric contents following an Ewald test meal. In recording the individual cell volume of case 13, no allowance was made for the increase of white blood cells which no

16. Persons, E. L.: Studies on Red Blood Cell Diameter: III. The Relation of the Diameter of Immature (Reticulocytes) and Adult Red Blood Cells in Health and Anemia, Especially in Pernicious Anemia, *J. Clin. Investigation* **7**: 615, 1929.

17. Fitzhugh, G., and Persons, E. L.: Studies on Red Blood Cell Diameter: IV. The Decrease in the Mean Diameter of the Reticulocytes and Adult Red Blood Cells in Pernicious Anemia Following Liver Therapy, *J. Clin. Investigation* **7**:631, 1929.

doubt influenced the figure. This case, as well as cases 15 and 23 and 23A, are recorded in table 9. Attention was called previously to the fact that many of this group of cases showed a high cell volume figure. Only in cases 23, 23A do the two figures agree as to the cell size. More determinations must be made in order to decide definitely whether or not there is actually an increase in red cell size in such cases.

In three cases (16, 17 and 24, table 12) the anemia was the result of acute loss of blood. Observations of both the individual cell volume

TABLE 12.—*Comparison of Mean Diameter with Individual Cell Volume in Miscellaneous Cases*

Case	Mean Diameter, Microns	Individual Cell Volume ($\times 10^{-11}$ Ce.)	Red Blood Cells in Millions Per C.Mm.	Hemo-globin in Grams per 100 Ce.	Diagnosis
1	6.47	11.5	1.22	2.48	Pregnancy and anemia
2	6.68	8.4	2.75	4.14	Carcinoma of stomach
3	7.00	6.7	3.76	5.94	Diaphragmatic hernia
4	7.12	8.1	5.56	14.90	No disease
5	7.13	7.0	5.72	12.90	Achylia gastrica
6	7.15	8.3	4.32	13.77	Gallstones; jaundice
7	7.16	8.2	3.40	8.28	Subacute bacterial endocarditis
8	7.18	9.3	4.28	12.02	Nutritional anemia
9	7.21	9.3	3.54	11.02	Arteriosclerosis
10	7.22	8.5	4.47	12.00	Gallstones; cirrhosis; jaundice
11	7.24	7.2	4.16	10.08	Erythema, nodosum
12	7.29	7.1	3.41	4.96	Fibroma of uterus
12A	7.35	7.0	3.31	4.83	Fibroma of uterus
13	7.34	10.0	1.70	5.16	Lymphatic leukemia
14	7.36	6.8	4.71	12.02	Carcinoma of colon
15	7.36	10.2	1.95	4.83	Leukemia, aleukemic myeloid
16	7.38	8.0	3.23	12.02	Duodenal ulcer
16A	7.73	10.1	2.68	8.14	Duodenal ulcer; acute hemorrhage
17	7.42	7.4	2.16	4.14	Hemorrhoids; acute hemorrhage; epistaxis
17A	7.59	9.9	3.13	8.28	Hemorrhoids; acute hemorrhage
17B	7.83	10.2	3.53	9.94	Hemorrhoids; acute hemorrhage
18	7.40	8.3	4.21	11.02	Myocarditis
19	7.68	7.0	4.70	7.86	Ulcer with hemorrhage
20	7.68	8.3	4.44	11.60	Ulcer with hemorrhage (question)
21	7.70	6.5	4.76	8.41	Ulcer with hemorrhage
21A	7.70	7.3	5.10	10.50	Ulcer with hemorrhage
22	7.76	8.0	4.25	9.94	No disease
23	7.98	9.3	1.81	3.86	Leukemia, aleukemic myeloid
23A	8.04	9.3	2.15	4.84	Leukemia, aleukemic myeloid
24	8.27	10.5	2.13	9.46	Carcinoma of stomach

and the mean cell diameter measurement made shortly following or during the period of loss of blood showed an increase in the size of the red blood cells. The figures obtained at this time are shown under 16A, 17B and 24 (table 12). Later, after the blood loss had ceased and the count was more nearly normal, the size was found to be essentially normal by both methods, as shown under 16 and 17 (table 12). In one observation (17A), the figures do not agree as to the size of the cells, the individual cell volume being larger than normal, whereas the mean diameter is within normal limits. This patient lost blood from time to time during the period of observation and repeated individual cell volume studies showed a figure greater than the normal range. This case is also listed in table 4 as case 12. As was mentioned

in the discussion of this table, the individual cell volume figure was larger than normal in most instances shortly after hemorrhage.

From an analysis of the figures in table 12, the evidence suggests that the individual cell volume determination is quite as reliable as is the measurement of the mean diameter by the methods used.

CONCLUSIONS

The determination of the individual cell volume as suggested by Haden and as herein recorded is a more simple means of determining the average cell size than is the measurement of the mean cell diameter.

Determinations of the individual cell volume are very helpful in differentiating pernicious anemia from other anemias in most instances in which difficulty in diagnosis might arise, the outstanding exception being in the rare condition, so-called aleukemic leukemia. During and shortly following acute loss of blood, there is an increase in the average individual cell volume, whereas in anemia resulting from chronic loss of blood, the individual cell volume is generally low.

Figures presented suggest that with adequate liver therapy, the red blood cells of patients with pernicious anemia return to normal volume. An individual cell volume figure greater than normal should indicate inadequate treatment.

Not only is the method for determining the individual cell volume a simple one to use, but the information so obtained is also as reliable as is that obtained by measurement of the mean diameter of the red blood cells by the method used.

Miss Isabel Howard aided with much of the technical work.

IRON METABOLISM IN PERNICIOUS AND IN SECONDARY ANEMIA *

HERMAN H. RIECKER, M.D.

WITH THE TECHNICAL ASSISTANCE OF MARY E. WINTERS, B.S.

ANN ARBOR, MICH.

For a long time it has been known that iron occurs in the blood in some other combination than with hemoglobin, and recent studies¹ have shown that this serum iron varies in quantity during iron starvation in experimental animals. In dogs rendered anemic by long-continued hemorrhage, with a limited intake of iron, the normal level of serum iron is reduced about 33 per cent, and when iron-containing foods or medicinal iron salts are given, the normal level returns, with consequent regeneration of the blood.

The object of this paper is to report clinical studies directed toward the application of these results to the problem of iron metabolism in pernicious anemia and secondary anemia in man.

METHODS

The method for determination of iron devised by Elvehjem and Hart² was adopted for this work, since its accuracy for small amounts of iron in biologic materials is unquestioned. One source of error in the determinations of serum iron is that a small amount of hemoglobin will vitiate the readings. This was

TABLE 1.—*Recovery of Iron from 10 Cc. Samples of Serum*

Sample	Initial Fe Content of Serum, Mg.	Added Iron, Mg.	Recovered after Precipitation, Mg.	Error
1.....	0.1	None	0.1
2.....	0.1	0.1	0.21	+0.01
3.....	0.1	0.05	0.15
4.....	0.1	0.04	0.137	-0.003
5.....	0.1	0.03	0.129	-0.001

controlled by precipitation of the serum proteins with 10 per cent trichloroacetic acid, according to a suggestion of Briggs.³ Other control studies on the method are reported in a previous paper. The accuracy of the method may be seen from table 1. It is advisable to use not less than 10 cc. samples for analysis, and when this has been done the method has been accurate, in my experience, to 0.02 mg. of iron.

* Submitted for publication, Feb. 28, 1930.

* From the Department of Medicine of the University of Michigan and the Thomas Henry Simpson Memorial Institute for Medical Research.

1. Riecker, H. H., and Winters, M. E.: Serum Iron Determinations Applied to the Study of Experimental Anemia, *Am. J. Physiol.* **92**:196 (Feb.) 1930.

2. Elvehjem, C. A., and Hart, E. B.: Iron in Nutrition: II. Quantitative Methods for the Determinations of Iron in Biological Materials, *J. Biol. Chem.* **64**:43, 1926.

3. Personal communication to the author.

IRON CONTENT OF NORMAL SERUM

In forty persons, I have found the iron content of the serum to be as shown in table 2. From this small group of normal people, the mean value of 1.1 ± 0.022 mg. per hundred cubic centimeters of serum is derived. It is probable that this figure varies somewhat, depending on the method used in determinations of iron, and with this in mind it would be useless to compare my results with those of the earlier investigators.

IRON CONTENT OF SERUM IN PERNICIOUS ANEMIA

With the advent of a method of producing a remission in pernicious anemia by means of liver extract, an opportunity was afforded for determining the iron metabolism in this disease somewhat more completely than had hitherto been possible. A complete study of the iron metabolism in pernicious anemia was made by Queckenstedt⁴ in 1914, in

TABLE 2.—*Values Found for Iron in the Serum of Normal Persons*

Iron per 100 Cc. Serum, Mg.	Persons
0.9.....	5
1.0.....	16
1.1.....	5
1.2.....	2
1.3.....	7
1.4.....	5
	<hr/> 40

which the literature to that date was reviewed. This investigator could find no evidence of destruction of blood by quantitative estimation of the iron in stools and urine in pernicious anemia. However, Kennerknecht⁵ in 1911 had found an excess excretion in the stools of several patients with pernicious anemia, amounting to from 15 to 20 mg. per day.

The "control" observations in my cases, preliminary to specific treatment, indicate that the total excretion of iron during relapse is approximately that of normal persons.

It was necessary to determine the iron content of the stools and urine of these patients over a long period of time in order to explain the changes which are found to take place in the level of the serum iron as remission of the disease takes place. Previous studies of the serum iron in pernicious anemia have been reported by Fowell,⁶ in which it was

4. Queckenstedt: Untersuchungen über den Eisenstoffwechsel bei der perniziösen Anämie mit Bemerkungen über den Eisenstoffwechsel überhaupt, Ztschr. f. klin. Med. **79**:49, 1914.

5. Kennerknecht, Klara: Beiträge zur Kenntnis des Eisenstoffwechsels bei perniziösen Anämie und Leukämia, Virchows Arch. f. path. Anat. **205**:89, 1911.

6. Fowell, P. H. C.: Iron in the Blood, Quart. J. Med. **6**:179, 1912.

concluded that the nonhemoglobin iron was much higher than normal, and that this fact might be of value in determining the extent of hemolysis in disease. Erben⁷ believed that the nonhemoglobin iron was increased in pernicious anemia, and I have been able to substantiate this in most instances, including that in which phenylhydrazine is used to produce hemolysis.

The serum from nineteen cases of pernicious anemia was analyzed for iron before and after induced remissions. Although there was a wide variation in the initial values, it is believed that in cases for which specific treatment had not been given, the iron levels of the serum were higher than normal. Table 3 gives a summary of the results together with the initial peripheral blood counts. In many of the cases, high

TABLE 3.—*Relation of the Initial Iron Content of the Serum to the Red Blood Cell Count in Pernicious Anemia*

Case	Initial Red Blood Cell Count, Millions	Initial Iron Content of Serum, Mg. per 100 Cc	Final Values
1..	1.4	1.63	1.10
2	1.3	1.3	1.00
3.	2.32	1.5	1.4
4	0.73	1.22*	1.2
5	1.99	1.8	1.9
6	2.52	1.2*	1.3
7	1.31	1.0*	1.3
8	1.6	1.1	0.94
9	1.1	1.5	1.0
10	2.12	2.0	1.6
11	1.03	1.03*	0.9
12	1.07	1.17*	1.11
13	1.36	1.1*	0.9
14	1.34	1.33	1.10
15	1.68	1.08*	0.92
16.	1.68	1.29	1.00
17	2.03	1.50	1.42
18.	3.17	1.42	1.02
19.	2.9	1.29	0.90

* Having normal initial values for the serum iron

initial values of the serum iron became normal when remission was established, while in several the values remained constantly normal throughout the period of observation.

Those of the first group with high initial levels of the serum iron include cases 1 (1.63 mg.), 2 (1.3 mg.), 3 (1.5 mg.), 5 (1.8 mg.), 9 (1.5 mg.), 10 (2 mg.), 14 (1.33 mg.), 16 (1.29 mg.), 17 (1.5 mg.), 18 (1.42 mg.) and 19 (1.29 mg.). In all of these, the level became progressively lower as the blood picture approached normal. However, in some there was not a regular decline in the values of the serum iron, and for this I have no explanation.

Eight of the cases did not show an elevation of serum iron when admitted to the hospital. These are cases 4 (1.22 mg.), 6 (1.2 mg.), 7

7. Erben, F.: Die chemische Zusammensetzung des Blutes bei perniziösen Anämie, Ztschr. f. klin. Med. 40:267, 1900.

(1 mg.), 8 (1.1 mg.), 10 (1.08 mg.), 11 (1.17 mg.), 12 (1.1 mg.) and 14 (1.08 mg.).

In table 4, the studies of the peripheral blood and the corresponding determinations of serum iron have been compared. The abnormally high initial values of the serum iron bring to mind the corresponding increased bilirubin in the blood serum and suggest the possibility that these substances are derived from the same source, that of hemolysis of immature erythrocytes in the bone-marrow.

TABLE 4.—*Iron Content of the Serum in Pernicious Anemia*

Patient	Date	Red Blood Cells	Hemo- globin (Sahli), %	Reticulo- cytes, %	Fe in Serum, Mg. per 100 Cc.	Medication
1	June 22	1,400,000	31	1.63	Hog stomach
	June 26	1.60	
	June 28	1.8	
	July 1	1.9	
	July 8	2,490,000	45	1.6	
	July 10	1.4	
	July 12	1.3	
	July 15	2,690,000	58	1.2	
	July 17	1.0	
	July 22	3,390,000	62	1.12	
	July 29	1.2	
	Aug. 2	3,400,000	69	1.2	
	Aug. 5	1.15	
	Aug. 9	1.12	
	Aug. 12	1.15	
	Aug. 15	4,660,000	77	1.10	
2	Feb. 2	1,300,000	28	1.0	Lilly liver extract
	Feb. 9	1.3	
	Feb. 11	1.3	
	Feb. 13	1.25	
	Feb. 14	1.3	
	Feb. 16	21.3	1.0	
	Feb. 18	1,630,000	27	3.5	
	March 11	3,140,000	52	
3	Jan. 7	2,320,000	54	0.5	1.5	Lilly liver extract
	Jan. 12	2,050,000	47	1.9	1.25	
	Jan. 14	3.7	1.3	
	Jan. 18	2,970,000	67	7.1	1.4	
	Jan. 20	6.6	
	Jan. 24	3,200,000	70	3.0	1.4	
4	July 2	730,000	19	1.5	Lilly liver extract
	July 6	1.22	
	July 10	1,060,000	26	14.9	1.20	
	July 12	1.33	
	July 15	1,370,000	28	11.8	1.2	
5	Aug. 5	1,990,000	23	1.5	Hog stomach
	Aug. 9	1.8	
	Aug. 12	1.9	
	Aug. 20	2,250,000	41	
6	July 10	2,520,000	52	0.4	
	July 12	1.2	
	July 19	1,890,000	55	3.8	1.1	
	July 22	1.3	
	July 23	1,780,000	48	5.9	
7	Feb. 15	1,310,000	25	1.0	Lilly liver extract
	Feb. 18	1,300,000	27	1.0	
	Feb. 20	0.9	
	Feb. 23	1.1	
	Feb. 25	1,620,000	40	1.2	
	Feb. 27	1.3	
	March 2	2,350,000	51	1.3	
8	July 15	1,600,000	32	1.1	Hog stomach
	July 17	1.1	
	July 19	2,160,000	43	1.3	
	July 22	1.23	
	July 29	3,240,000	62	0.94	

TABLE 4.—*Iron Content of the Serum in Pernicious Anemia—Continued*

Patient	Date	Red Blood Cells	Hemo- globin (Sahli), %	Reticulo- cytes, %	Fe in Serum, Mg. per 100 Cc.	Medication
9	Feb. 12	1,100,000	21	2.0	1.5	Lilly liver extract
	Feb. 14	1,250,000	25	2.3	0.9	
	Feb. 18	9.5	1.3	
	Feb. 21	2,120,000	34	25.9	1.1	
	Feb. 25	0.9	
	Feb. 27	2,340,000	38	0.875	
	March 1	0.9	
	March 9	3,400,000	65	1.0	
10	June 12	2,120,000	50	0.8	Lilly liver extract
	June 19	2.0	
	June 24	2,340,000	46	6.9	1.43	
	June 26	3,080,000	55	5.7	1.6	
11	Nov. 19	1,030,000	27	2.3	1.08	Hog stomach
	Nov. 22	1.09	
	Nov. 25	1,200,000	24	2.3	1.08	
	Nov. 29	0.98	
	Dec. 3	1,080,000	22	7.4	0.90	
12	Sept. 10	1,070,000	20	2.0	1.17	Hog stomach
	Sept. 12	1.1	1.17	
	Sept. 14	1.6	1.19	
	Sept. 18	890,000	20	0.7	1.22	
	Sept. 20	0.8	1.23	
	Sept. 23	3.1	1.22	
	Sept. 26	920,000	20	9.1	1.5	
	Sept. 30	700,000	18	1.6	1.3	
	Oct. 2	1.0	1.04	
	Oct. 4	1.3	1.02	
	Oct. 7	68,000	17	0.9	1.02	
	Oct. 11	1.02	
	Oct. 14	98,000	20	28.1	1.02	
	Oct. 19	0.9	1.11	
	Oct. 22	1,350,000	34	1.0	1.13	
	Oct. 25	1,510,000	33	2.1	1.11	
13	Oct. 11	1,360,000	30	1.6	1.1	Hog stomach
	Oct. 19	1,280,000	30	0.5	1.12	
	Oct. 22	2.0	1.0	
	Oct. 25	0.89	
	Oct. 26	1,520,000	36	17.0	
	Oct. 29	1,780,000	42	12.8	1.13	
	Nov. 4	1.8	1.13	
	Nov. 5	2,100,000	50	2.2	
14	Nov. 15	700,000	17	1.4	Lilly's liver extract
	Nov. 22	1,340,000	20	40.9	1.33	
	Nov. 25	21.4	1.33	
	Nov. 29	2,400,000	39	9.3	1.10	
	Dec. 2	3,160,000	44	8.2	
15	Nov. 20	1,680,000	42	3.5	1.08	Hog stomach
	Nov. 22	3.7	1.07	
	Nov. 25	1,160,000	34	2.0	1.08	
	Nov. 29	2.7	0.9	
	Dec. 2	1,430,000	39	5.7	0.92	
16	Nov. 20	1,680,000	32	2.3	1.29	Parke Davis & Co. liver extract
	Nov. 22	1.3	1.29	
	Nov. 25	2,010,000	44	19.3	1.28	
	Nov. 29	1.00	
	Dec. 2	2,660,000	49	4.9	
17	Sept. 4	2,080,000	42	15.2	1.50	Lilly's liver extract
	Sept. 6	18.5	1.50	
	Sept. 9	1.50	
	Sept. 14	2,600,000	61	3.1	1.46	
	Sept. 16	2,880,000	61	0.7	1.42	
18	Sept. 6	1.42	Lilly's liver extract
	Sept. 9	3,170,000	65	5.1	1.3	
	Sept. 4	0.9	1.20	
	Sept. 16	3,640,000	65	1.4	1.03	
	Sept. 20	4,130,000	79	1.02	
19	Sept. 30	2,900,000	65	6.7	1.29	Lilly's liver extract
	Oct. 2	1.26	
	Oct. 4	2,830,000	64	1.9	1.20	
	Oct. 7	2,740,000	57	0.1	1.20	
	Oct. 14	3,080,000	68	7.7	0.90	

METHOD FOR DETERMINATION OF IRON METABOLISM IN
PERNICIOUS ANEMIA

For determination of the iron metabolism in pernicious anemia, six patients were selected who had been given no specific treatment. They were placed in bed under strict surveillance as to food and water intake and the collection of specimens. A diet was designed to contain 7.5 mg. of iron based on Shermans' analyses, and the foods prepared with distiller water.⁸

After a control period of between four and eleven days on the diet, the usual remission with liver extract was induced.

Stools were collected in white porcelain pails, pooled into five day lots (except when otherwise indicated) and dried over a steam bath. The total pooled specimen was then removed by a hard-wood spatula, the container being scraped with a porcelain spatula, and the specimen weighed. It was then ground to dust in a large porcelain mortar over which a rubber membrane had been attached. From this a sample was taken for analysis.

Collections of urine were made in the usual manner, pooled, measured, and samples analyzed corresponding to the collections of stools.

During the progress of the remission, it was necessary to increase the caloric value of the diet; this was done in a definite manner, and the increased content of iron was noted.

In the case of the two female patients, the collections of urine were not complete, but even here the results differed only in degree from those in the remainder of the series.

On several occasions, duplicate diets were prepared; one was fed to the patient and the other was dried, ground and analyzed for iron as a control measure. The results for calculated and chemically determined iron were close.

A patient with mild arthritis deformans was placed on the standard regimen, and the intake and the excretion of iron were found to balance during a ten day period. In none of the patients was there occult blood in the stools. Duplicate samples from the specimens of stools and urine were analyzed, and the results for iron used in derivation of the average figure, and in all cases medication of any nature was noted and analyzed and the result for iron added to the iron intake.

IRON METABOLISM IN PERNICIOUS ANEMIA

Case 1 was followed for a period of seventy-one days, during which the hemoglobin level (Sahli) rose from 28 per cent to 78 per cent, and the erythrocyte count from 1,020,000 to 4,570,000. During this period, the patient excreted 1,274.74 mg. of iron. His total intake of iron as food and in the liver extract was 634.28 mg., giving an excess excretion of 640.36 mg. The excretion was not constant and appeared greatest at the beginning of the second half of the period, that is, one month after treatment had begun.

8. Peterson, W. H., and Elvehjem, C. A.: Iron Content of Plant and Animal Foods, *J. Biol. Chem.* **78**:215 (June) 1928. Sherman, Henry: *Chemistry of Food and Nutrition*, New York, The Macmillan Company, 1927.

In case 2, the determinations were carried out over a period of thirty-four days; the hemoglobin level increased from 25 per cent to 88 per cent. The disease was of shorter duration than that of the previous patient and the patient was younger. He also had an exophthalmic goiter. However, the excess excretion was 297.3 mg., while the

TABLE 5.—*Iron Excretion During Active Remission in Case 1*

Dates, 1929	Excretion of Iron in Stool, Mg.	Excretion of Iron in Urine, Mg.	Total Excretion for Period, Mg.	Average Daily Excretion, Mg.	Food Iron Intake Daily, Mg.	Daily Excess Excretion, Mg.
Aug. 28-29.....	8.31	6.77	15.10	7.55	7.5	0.50
Aug. 30-31.....	8.06	8.05	16.11	8.05	7.5	1.55
Treatment with Liver Extract Began						
Sept. 1-5.....	26.89	21.26	48.15	9.63	7.5	2.13
Sept. 6-10.....	46.00	36.01	82.01	16.40	7.5	8.90
Sept. 11-15.....	63.27	37.88	101.15	20.23	7.5	12.70
Sept. 16-20.....	82.22	29.46	111.68	22.33	9.5	12.83
Sept. 21-25.....	36.56	27.54	64.10	12.82	10.0	2.82
Sept. 26-30.....	42.10	27.98	70.08	14.00	11.0	3.00
Oct. 1-5.....	37.98	42.26	80.24	16.05	12.5	3.55
Oct. 6-10.....	78.54	43.36	121.90	22.40	12.5	9.90
Oct. 11-15.....	71.96	30.83	102.79	20.56	12.5	8.06
Oct. 16-20.....	47.32	31.41	78.73	15.74	12.5	3.20
Oct. 21-25.....	66.70	36.88	103.58	20.71	10.0	10.71
Oct. 26-30.....	32.90	98.96	131.86	26.40	10.0	16.40
Oct. 31-Nov. 4.....	62.66	26.00	88.66	17.73	10.0	7.73
Nov. 5-7.....	39.72	18.84	58.56	19.52	10.0	9.52
Totals †.....	751.19	523.49	1,274.74		575.0	699.77

† Hemoglobin level rose from 23 per cent to 78 per cent and the red blood cell count from 1,020,000 to 4,570,000.

Iron in Lilly extract, 59.28 mg., subtracted from total excretion leaves excess excretion of 640.42 mg.

TABLE 6.—*Iron Excretion During Active Remission in Case 2*

Dates, 1929	Excretion of Iron in Stool, Mg.	Excretion of Iron in Urine, Mg.	Total Excretion for Period, Mg.	Average Daily Excretion, Mg.	Food Iron Intake Daily, Mg.	Daily Excess Excretion, Mg.
Oct. 26-30.....	59.2	32.7	31.9	18.40	7.5	10.9
Oct. 31-Nov. 4.....	44.9	20.9	65.8	13.60	7.5	5.6
Nov. 5-9.....	27.4	43.4	70.8	14.16	7.5	6.6
Nov. 10-14.....	40.1	43.3	83.4	16.70	8.0	8.7
Nov. 15-19.....	48.0	33.0	81.0	16.02	10.0	6.0
Nov. 20-24.....	84.9	31.6	116.5	25.30	12.0	13.3
Nov. 25-28.....	77.7	34.6	112.3	28.08	12.5	16.5
Totals for 34 days †.....	382.2	239.5	621.7		312.5	309.2

† Hemoglobin level rose from 25 per cent to 88 per cent and the red blood cell count from 940,000 to 5,600,000.

Iron in Lilly extract, 11.85 mg., subtracted from total excretion leaves excess excretion of 297.35 mg.

total iron intake was 324.3 mg. He was still excreting large quantities of iron when referred for operation for exophthalmic goiter.

Case 3 was observed for a period of eighteen days, four of which were in the control period. The hemoglobin level rose from 40 per cent to 50 per cent. The patient's excess excretion of iron amounted to 107.45 mg. The marine liver extract used in this case contained 275

mg. of iron. On account of the short period of observation there was a low excess excretion of iron.

In case 4, observed for twenty-three days, an excess excretion of 162.38 mg. of iron was obtained, although the patient had not been under observation a sufficiently long time to obtain a true metabolic picture.

Case 5 was observed during a fifty-one day period. The collections of urine were incomplete throughout, but an excess excretion of 126.62 mg. of iron was found. The liver extract contained 343.95 mg. of iron,

TABLE 7.—*Iron Excretion During Active Remission in Case 3*

Dates, 1929	Excretion of Iron in Stool for Period, Mg.	Excretion of Iron in Urine for Period, Mg.	Total Excretion for Period, Mg.	Average Daily Excretion, Mg.	Average Food and Medicine Iron Intake Daily, Mg.	Average Daily Excess Excretion, Mg.
Feb. 22-23-24.....	31.6	8.70	40.30	13.40	8.71	4.69
Feb. 25.....	8.4	8.80	17.20	17.20	9.43	17.77
Treatment with Liver Extract Began						
Feb. 26-March 2.....	107.9	14.30	122.20	24.40	23.76	0.64
March 3-7.....	141.0	17.80	158.80	31.76	26.01	5.75
March 8-13.....	159.6	33.49	193.09	38.62	27.93	10.69
Totals †.....	448.5	83.09	531.59		424.06	107.43

† Hemoglobin level rose from 40 per cent to 50 per cent and the red blood cell count from 1,410,000 to 2,180,000.

Marine liver extract used, containing 275.4 mg. iron.

TABLE 8.—*Excretion of Iron in Case 4*

Dates, 1929	Excretion of Iron in Stool for Period, Mg.	Excretion of Iron in Urine for Period, Mg.	Total Excretion for Period, Mg.	Average Daily Excretion, Mg.	Average Daily Food Iron Intake, Mg.	Average Daily Excess Excretion, Mg.
March 19-21.....	68.50	9.50	78.00	26.00	9.67	16.33
March 22-24.....	29.40	15.00	44.40	13.93	9.94	3.99
March 25-27.....	39.00	8.10	47.10	15.70	10.22	5.48
March 28-30.....	24.60	12.10	36.70	12.23	10.62	1.61
March 31-April 2.....	33.40	12.84	36.24	12.08	9.56	2.52
April 3-7.....	81.76	25.70	107.46	21.49	10.80	10.69
April 8-12.....	54.12	21.26	75.38	15.07	12.18	2.89
Totals †.....	320.78	104.50	425.28		246.94	178.34

† Hemoglobin rose from 51 per cent to 63 per cent and the red blood cell count from 2,020,000 to 2,540,000.

Iron in liver extract, 15.96 mg.; subtracted leaves excess excretion, 162.38 mg.

and under a more rigidly reduced intake of iron a much higher excretion would have been obtained.

Case 6 was observed forty-six days, during which the hemoglobin level rose from 24 to 67 per cent. The excess excretion of iron was 196.76 mg. The elimination of relatively large amounts of iron during remission agrees with the recent observation of pathologists that hemosiderosis has been conspicuously absent in the tissues of patients dying during a remission induced by liver extract.

IRON METABOLISM IN SECONDARY ANEMIA

Studies of the serum iron were made on twenty cases of various types of secondary anemia and two cases of polycythemia vera.

An attempt was made to answer the following questions: 1. Is there evidence of iron starvation in certain types of secondary anemia? 2. Does

TABLE 9.—*Iron Excretion During Active Remission in Case 5*

Dates, 1929	Excretion of Iron in Stool for Period, Mg.	Excretion of Iron in Urine for Period, Mg.*	Total Excretion for Period, Mg.	Average Daily Excretion, Mg.	Average Daily Food Iron Intake, Mg.	Average Daily Excess Excretion, Mg.
Jan. 31-Feb. 4.....	33.95	15.90	49.85	9.97	6.76	3.21
Feb. 5-6.....	24.16	8.60	32.76	16.38	6.45	9.93
Treatment with Liver Extract Began						
Feb. 7-10.....	56.90	14.38	71.28	17.82	5.95	11.87
Feb. 11-15.....	42.30	11.84	54.14	10.83	6.82	4.01
Feb. 16-20.....	49.95	18.42	68.37	13.67	7.03	6.64
Feb. 21-25.....	106.70	24.70	131.40	26.26	6.90	19.36
Feb. 26-March 2.....	67.90	13.70	81.60	16.32	6.88	9.94
March 3-7.....	65.30	13.95	82.25	16.45	6.17	10.28
March 8-12.....	58.20	15.59	73.79	14.76	8.19	6.57
March 13-17.....	63.60	16.25	79.85	15.97	8.43	7.54
March 18-22.....	84.40	17.45	101.85	20.37	10.19	9.88
March 23-28.....	56.00	28.10	84.10	14.01	11.25	2.76
Totals †.....	712.36	198.88	911.24		440.67	470.57

* Urine collection incomplete throughout.

† Hemoglobin level rose from 40 per cent to 79 per cent and the red blood cell count rose from 1,800,000 to 4,470,000.

Iron in liver extract, 343.95 mg., subtracted leaves 126.62 mg. excess excretion.

TABLE 10.—*Excretion of Iron in Case 6*

Dates, 1929	Excretion of Iron in Stool for Period, Mg.	Excretion of Iron in Urine for Period, Mg.*	Total Excretion of Iron for Period, Mg.	Average Daily Excretion, Mg.	Average Daily Food Iron Intake, Mg.	Average Daily Iron Excess, Mg.
Feb. 15-19.....	89.54	23.03	112.57	22.51	5.78	16.73
Feb. 20-24.....	57.90	21.25	79.15	15.83	5.76	10.07
Treatment with Liver Extract Began						
Feb. 25-March 1.....	20.10	25.32	45.62	9.12	5.87	3.25
March 2-6.....	41.40	18.76	60.16	12.03	6.30	5.73
March 7-11.....	54.40	15.55	69.95	13.99	8.54	5.45
March 12-16.....	33.60	9.95	43.55	8.71	10.05	-1.34
March 17-21.....	104.50	16.38	120.88	24.18	9.80	14.38
March 22-26.....	87.00	21.72	108.72	21.74	9.59	12.15
March 27-April 1.....	57.90	23.50	81.40	13.56	9.94	3.62
Totals †.....	546.34	175.66	766.00			353.87

* Collection of urine incomplete throughout.

† Hemoglobin rose from 24 per cent to 67 per cent and the red blood cell count from 1,000,000 to 3,530,000.

Iron in liver extract, 157.08 mg.; subtracted leaves excess excretion, 196.79 mg.

iron medication influence the level of the serum iron? 3. Is there a relationship between the level of the serum iron and that of hemoglobin in these conditions?

Iron starvation most likely would be found in patients presenting a history of long-continued bleeding from the gastro-intestinal tract. How-

ever, a large number fail to show it because iron medication or a diet rich in iron had been used in their treatment. I have studied two cases of peptic ulcer, nos. 3 and 10, with initial values of serum iron below the average normal and almost as low as in experimental animals under

TABLE 11.—Iron Content of the Serum in Secondary Anemias

Patient		Date	Red Blood Cells	Hemo- globin (Sahli), %	Reticulo- cytes, %	Fe in Serum Mg. per 100 Cc.	Medication
1	Myxedema	Sept. 23	3,300,000	52	...	1.94	Thyroid extract
		Sept. 25	3,210,000	52	...	1.7	
2	Secondary anemia; gallstones	July 2	3,310,000	43	...	1.0	10% solution ferrie ammonium citrate three times a day
		July 8	3,670,000	46	...	1.26	
		July 12	3,310,000	54	...	1.3	
		July 23	4,500,000	48	...	1.45	
		Aug. 6	4,890,000	61	2.8	
3	Duodenal ulcer	May 9	3,210,000	65	"High iron" diet
		May 11	0.9	
		May 14	4,100,000	71	...	0.85	
		May 17	4,380,000	70	...	1.0	
4	Rectal bleeding	Oct. 19	1.09	Iron medication
		Oct. 25	1.33	
		Nov. 1	1.29	
5	Menorrhagia	June 3	4,270,000	32	...	2.4	4 Gm. ferrie am- monium citrate daily
		June 6	4,230,000	33	...	2.6	
		June 8	1.4	
		June 14	4,300,000	33	...	1.6	
6	Cancer of cecum	Feb. 2	2,950,000	20	...	1.0	None
		Feb. 4	2,590,000	15	...	0.94	
		Feb. 6	1.0	
		Feb. 8	2,310,000	15	...	1.3	
7	March 15	2,630,000	26	...	1.1	No iron
8	June 24	1,660,000	20	...	1.18	50% solution of ferrie ammonium citrate, 4 cc. three times daily
		July 8	2,700,000	31	...	1.6	
9	Cancer of stomach	May 29	2,710,000	30	...	1.33	Iron medication as above
		June 9	20	...	1.4	
10	Bleeding septic ulcer	April 25	2,780,000	45	2.0	0.8	Began with 50% solution of ferrie ammonium citrate, 8 cc. three times daily
		April 26	
		April 27	2,780,000	41	1.5	0.8	
		April 29	2,910,000	37	1.9	0.8	
		May 3	3,220,000	42	2.1	0.9	
		May 6	3,870,000	43	3.2	1.0	
		May 13	4,160,000	51	3.4	1.2	
11	Duodenal ulcer	May 10	3,350,000	50	Ferrie ammonium citrate on May, 20, 1929
		May 11	1.5	
		May 24	1.7	
		May 31	1.7	
		June 3	2,000,000	40	
12	Aplastic anemia	Jan. 19	660,000	16	...	1.3	Blaud's pills; transfusions
		Jan. 22	640,000	15	...	1.2	
		Jan. 28	730,000	15	...	1.2	
		Feb. 1	1.2	
		Feb. 3	1.1	
		Feb. 6	850,000	31	...	1.1	
13	Ulcer of stomach	Feb. 16	1,910,000	22	...	1.7	Ferrous iodide 4 cc. three times daily; discontinued; trans- fusions Feb. 17 and 21
		March 4	2,700,000	50	...	1.5	
		March 8	1.3	
		March 15	1.1	
14	Cancer of stomach	Feb. 4	1,940,000	15	...	1.9	Transfusion
		Feb. 6	2,650,000	24	...	1.8	
		Feb. 9	1.0	
		Feb. 11	1.0	
		Feb. 15	2,980,000	26	...	1.5	
15	Jan. 10	40	...	1.55	Iron; blaud's pills
		Jan. 14	3,650,000	41	...	1.24	
		Jan. 22	3,270,000	40	...	1.3	
		Feb. 7	3,730,000	42	...	1.4	
		Feb. 20	4,150,000	52	...	1.4	

similar conditions. The first case gave an initial value of 0.9 mg. and the second 0.8 mg., and under iron medication these figures became normal or above normal. It might be supposed that the serum iron increased as the patient improved, but in other cases an initial high value of iron was found, and besides in the experimental anemia no such relationship was apparent.

Of two patients with polycythemia, one had a high level of the serum iron (1.80, 1.75) while under treatment with phenylhydrazine, and the other a level much below the average normal (0.86 mg.). The latter was treated by repeated venesection while on a diet containing a minimum amount of iron. These values are interesting but capable of anticipation in view of the contrasting forms of treatment utilized.

In a case of menorrhagia (no. 5; hemoglobin 32 per cent, red blood cells 4,270,000) and one of duodenal ulcer (no. 11; hemoglobin 50 per cent, red blood cells 3,350,000) for which iron had been given as medication, the levels of the serum iron were much higher than normal, thus indicating that the iron content of the serum can be materially raised by such a procedure. In case 4, the level of the serum iron was raised from a normal of 1.09 to 1.33 mg. by iron as medication.

Of four children with so-called nutritional anemia, two were found to have low and two normal levels of the serum iron. They all improved without the use of medicinal iron.

A summary of the data for the cases of secondary anemia is given in table 11.

COMMENT

Determination of the iron content of the blood serum may have practical clinical value in all forms of anemia, and various types of medication may be studied with reference to absorption by this means. It is believed that the color index should be of value in determining the necessity for medicinal iron, and in my experience patients with low color indexes respond best, and these are most often found to have relatively low levels of the serum iron. However, such conditions as carcinomatosis, with a low color index, show a high level of the serum iron, and in these medicinal iron can have no value.

It is known, then, that clinical, as well as experimental, iron starvation is reflected in the level of the serum iron, and that feeding iron in any form increases this level. This conclusion is based only on clinical evidence, for when iron is administered in the experimental anemia of hemorrhage, regeneration of hemoglobin results immediately. I can find no direct relationship between the level of the serum iron and that of hemoglobin, since this is governed by other factors. However, it might be said that cases of secondary anemia due to iron starvation are comparatively rare, and that the indication for medicinal iron likewise

is seldom present. Unpublished data in my possession indicate that the form or compound of iron used has no appreciable significance and that animal experiments purporting to show this cannot be successfully applied clinically.

It is not known in what form the iron occurs which is not combined as hemoglobin, and Fowell⁶ discussed this problem in his excellent study. He believed that minute quantities of inorganic iron are highly toxic in the blood stream and assumed that the compound must be in either colloidal or organic form. I have analyzed spinal fluid and found just an appreciable amount of iron (0.4 mg. per hundred cubic centimeters), hence it might be presumed that the serum iron is partially nondiffusible. That it is not in combination with protein is shown by the method of precipitating the protein of the serum before making the analyses. It is possible that several compounds are present. The problem has interesting possibilities.

CONCLUSIONS

1. There is present in blood serum a partly diffusible iron compound the estimation of which may be used to determine the presence and degree of iron starvation in disease and likewise the effect of iron medication.

2. The amount of serum iron is increased in hemolytic diseases of the blood and decreased in the presence of long continued hemorrhage or a dietary deficiency of iron.

3. In pernicious anemia, the level of the serum iron usually is higher than normal but becomes normal during remissions in the disease.

4. A remission in pernicious anemia is accompanied by an increase in excretion over the intake of iron, as determined by analyses of stool and urine.

5. In secondary anemia, one rarely finds as marked iron starvation as in experimental hemorrhage in animals on a diet low in iron, and from this standpoint alone, the indications for medicinal iron are limited.

THE SIGNIFICANCE OF AN ELECTROCARDIOGRAM WITH A LARGE Q IN LEAD 3*

HAROLD E. B. PARDEE, M.D.

NEW YORK

The presence of a large Q wave in the third lead is frequently observed in electrocardiographic records from patients with the anginal syndrome. In the majority of these records the QRS group shows left axis deviation, though in a few the electrical axis has a normal direction. The frequency of the large Q-3, both in cardiac patients in general and in those with the anginal syndrome in particular, will appear from the following: In a series of 200 cases of heart disease of various sorts recorded alphabetically in a file of office patients, 30 showed a diagnosis of the anginal syndrome, including both the angina of effort and the angina appearing at rest.¹ Of these 30 patients with the anginal syndrome 8, or 27 per cent, were found to have a large Q wave in the third lead. In the other 170 cases 6 such records were found; so that the peculiarity in question occurred in patients with heart disease without the anginal syndrome with a frequency of only 3.5 per cent.

In any discussion of the height of one of the QRS deflections one must take into account the maximum voltage of the QRS group as shown by the amplitude of the largest wave of this group in whichever lead this may occur. For example, the current producing a Q wave of 3 mm. in lead 3 is a less important part of a QRS group the largest excursion of which is an R-2 of 18 mm. than it is of one the largest deflection of which is an R-2 of 5 mm. In the first case the Q bears only an insignificant relation to the largest current of QRS, while in the second case the current producing Q is more than half as large as the maximum produced. It became necessary, then, to decide what should be considered a large Q wave. After considerable inspection and examination of various records, it seemed that if 25 per cent of the maximum excursion of QRS, in whichever lead this appeared, were considered as the dividing line between large and small Q waves, there would be little danger of applying the term abnormal to a wave that was really normal. In examining the records of fifty-two normal persons,

* Submitted for publication, Feb. 1, 1930.

* From the New York Hospital and the Department of Medicine of the Cornell University Medical School.

1. Vaquez, H., and Laidlaw, George F.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1924. Criteria Committee of New York Tuberculosis and Health Association: Criteria for the Classification and Diagnosis of Heart Disease, New York Tuberculosis and Health Association, 1929.

Lewis and Gilder² found that the largest Q wave in lead 3 measured 2.5 mm. The amplitude of Q-3 in this series was always less than 25 per cent of the amplitude of the largest R of the record.

In addition to a Q wave in the third lead that was more than 25 per cent of the largest excursion of QRS, the records under consideration (fig. 1) show either left axis deviation of QRS with R-1 greater than R-2 or, more rarely, a normal direction of the axis of QRS with R-2 larger than either R-1 or R-3. Records showing R-3 larger than R-2 were not included in this study, for Q-3 is a normal feature of records showing right axis deviation. In certain records there is a small Q in

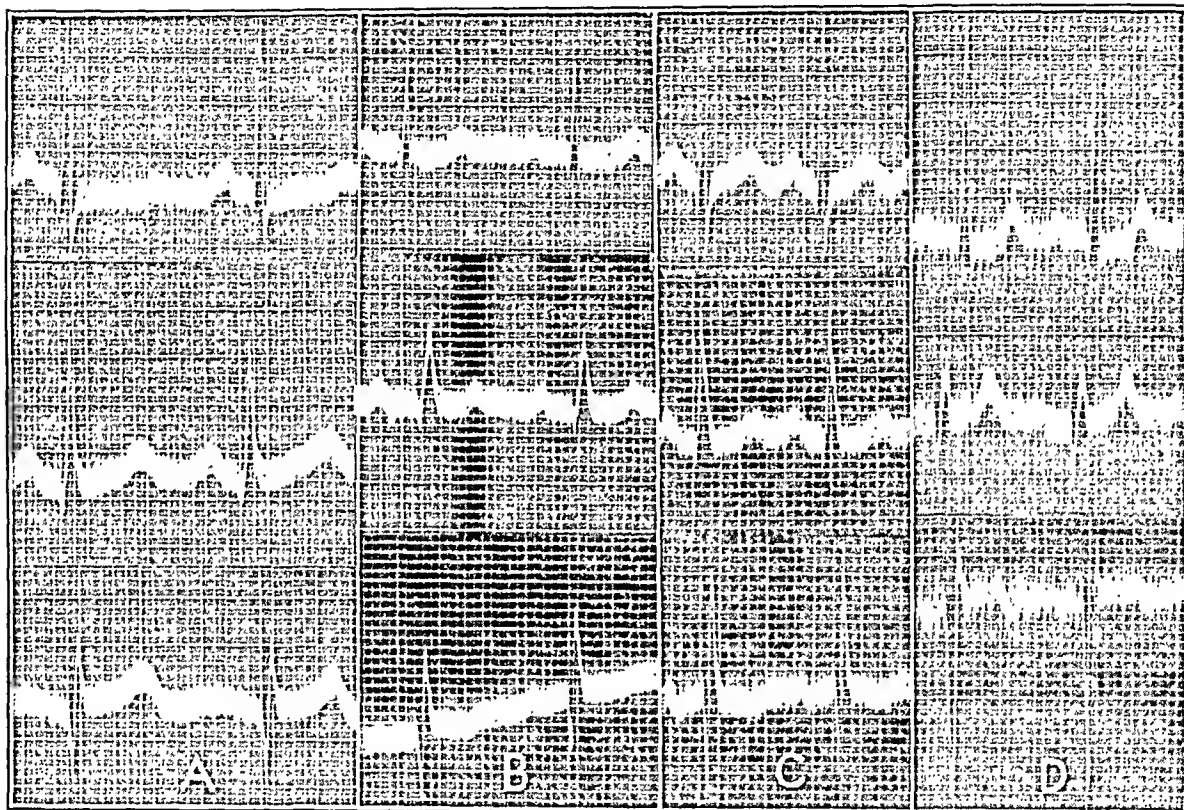


Fig. 1.—Four of the records showing a large Q wave in lead 3.

lead 1, and possibly in lead 2 as well; often Q-2 is larger than Q-1. There is often a fair-sized S wave in lead 1, and when S is absent from lead 1 it does not appear in lead 2. The least frequent of these waves is S-2 (8 times). The others appear with about equal frequency: Q-1, 21 times; S-1, 29 times, and Q-2, 27 times. The most frequent combinations are Q-1, S-1 and Q-2 (11 times), S-1 and S-2 (8 times) and Q-1 and Q-2 (5 times); no Q or S appears in either lead in 4 instances.

2. Lewis, T., and Gilder, M. D. D.: The Human Electrocardiogram: A Preliminary Investigation of Young Adults to Form a Basis for a Pathological Study, Phil. Tr. Roy. Soc. London 202:351 (March) 1912.

The T wave in these records is often normal (63 per cent of the forty-three studied) ; either upward in all leads (28 per cent) or upward in leads 1 and 2 and downward in lead 3 (35 per cent). It is often found upward in lead 1 and downward in leads 2 and 3 (25 per cent), and occasionally downward in leads 1 and 2 and upward in lead 3 (9 per cent). One patient (2.5 per cent) had a downward T-1, with an upward T-2 and T-3; none had a downward T in all leads. It is an interesting fact that of the sixteen patients (see accompanying table) with a large Q-3 who did not have the anginal syndrome, only one had an abnormal T wave (this was downward in leads 1 and 2, and upward

Frequency of Large Q-3 in Patients with Cardiac Disease

	Large Q 3	Small Q 3
Anginal syndrome	27 (63%)	2 (7%)
Syphilitic aortic insufficiency	1	0
Myocardial fibrosis		
With congestion	4	0
With arrhythmia	1	0
Rheumatic heart disease		
Active, with mitral insufficiency	1	0
Aortic insufficiency, with or without mitral disease	2	3
Mitral insufficiency	0	2
Mitral stenosis, with or without mitral insufficiency	1	3
Arteriosclerosis with hypertension	1	2
Hypertension with arrhythmia	1	2
Hyperthyroid (enlarged heart), enlargement on percussion and by roentgenograms; patient 54 years of age	1	0
Pregnancy, a record after delivery did not show a large Q-3 (normal heart)	1	0
Effort syndrome, including the group of cases showing neurocirculatory asthenia (normal heart)	2	7
Normal heart	0	5
Congenital heart defect	0	1
Arteritis obliterans	0	1
	43	28

in lead 3). The greater frequency of inversion of T-2 and T-3 (25 per cent) as compared with T-1, with or without T-2 (11.5 per cent), is noteworthy.

Through Dr. A. E. Cohn it was possible to review the electrocardiograms of 160 normal soldiers³ taken at the Hospital of the Rockefeller Institute. Four records were found with a large Q-3 of a value of 25 per cent or more of the largest wave of the QRS group. Two of these showed right axis deviation of QRS and so were not the type of record here under consideration. The other two were of the type shown in figure 1; one of them had slight left axis deviation of QRS and an inverted T-3, while the other showed a normal direction of the electrical axis with T upward in all leads. Another series of records of sixty-five normal hearts, taken at the clinic of the Cornell Medical School, was

3. Cohn, A. E.: An Investigation of the Size of the Heart in Soldiers by the Teleroentgen Method, Arch. Int. Med. 25:499 (May) 1920.

made available by Dr. A. M. Master. No records with a large Q-3 were found in this group, nor was there any in the fifty-two records of Lewis' series² which he loaned to me for examination. Thus, only two records of this peculiar type were found in the 277 records from normal hearts.

In the course of selecting these records, many were found of the type seen in figure 2, with a downward deflection in lead 3 followed by an upward deflection and then another downward deflection, so that in this lead the QRS group had somewhat the shape of the letter W. Other records were observed in which there was a small upward deflection

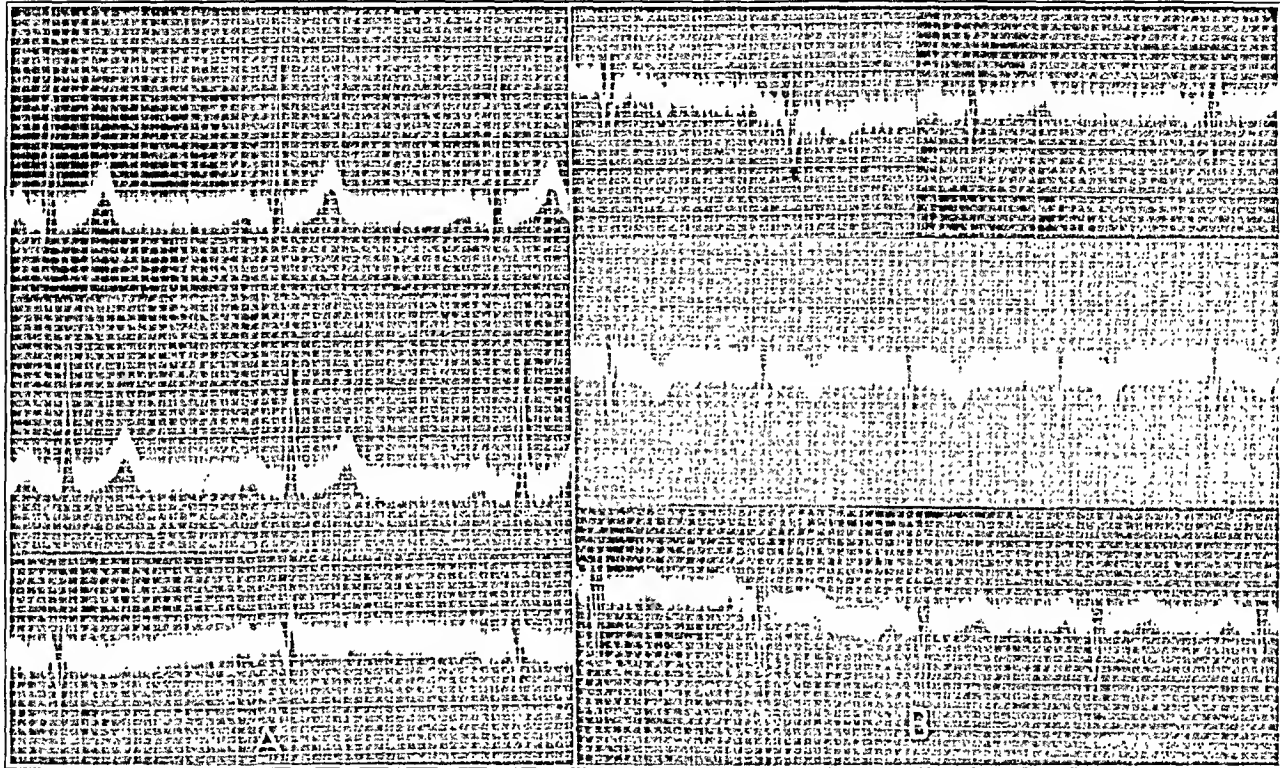


Fig. 2.—A, record showing the M type of complex in lead 3; B, lead 3 of four records, showing M or W type of complexes.

followed by a larger downward deflection and then another upward deflection, so that the QRS had somewhat the shape of a deformed letter M. In other records the QRS in lead 3 was even more definitely vibratory. All such records were excluded, the only ones considered being those that conformed strictly to the type seen in figure 1, having in lead 3 an initial downward deflection (Q) followed by a definite upward deflection (R), without an S wave.

For comparative study a group of twenty-eight records was selected from the same file, having a small Q wave in lead 3 according to the arbitrary standard used, i.e., less than 25 per cent of the maximum excursion of QRS in whichever lead this appeared, but which conformed

to the other features described for the records with a large Q-3. These records (fig. 3) showed either left axis deviation or QRS or a normal direction of the axis; they often had an S in lead 1, but never an S in lead 3. Q was present in lead 1, lead 2 or both. Such records were perhaps two and one-half or three times as frequent as those showing a large Q-3.

A comparison of the clinical diagnoses in forty-three cases showing a large Q-3 with the diagnoses in twenty-eight cases with a small Q-3 appears in the accompanying table. It will be seen that 63 per cent of the patients showing a large Q-3 were found to be suffering from the

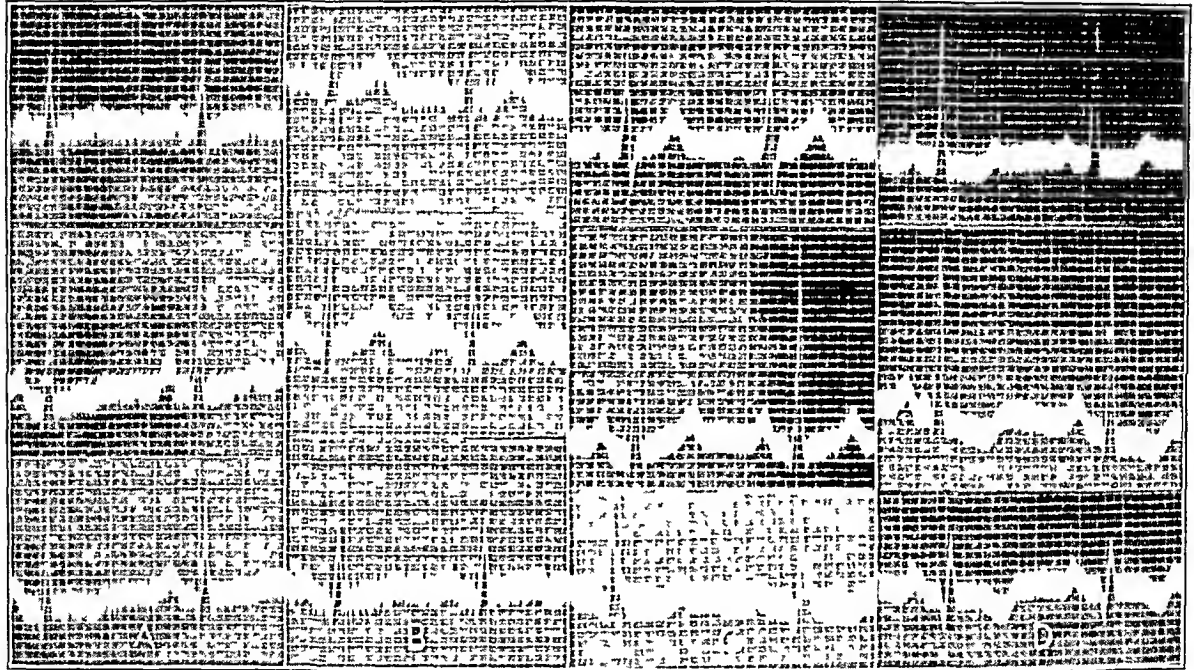


Fig 3—Four records showing a small Q wave in lead 3.

anginal syndrome, whereas only 7 per cent of those with a small Q-3 had this complaint. The pathologic changes underlying the anginal syndrome are admittedly various, but it is generally agreed that occlusion, or at least marked narrowing, of a coronary branch is the most frequent cause of the angina of rest, and that coronary narrowing without occlusion is probably the most frequent cause of the angina of effort. A review of the other diagnoses in the table reveals syphilitic aortitis with aortic insufficiency, myocardial fibrosis and rheumatic aortic insufficiency, all conditions that might well be associated with coronary narrowing. If the eight cases with these diagnoses are added to the twenty-seven with an anginal syndrome, one has a total of thirty-five, or 81 per cent of the group with a large Q-3. In this 81 per cent the underlying pathologic process is probably the narrowing of a coronary

branch or branches. If one adds together the same types of cases in the group with a small Q-3 one has five, or 17 per cent of the total.

If one selects from the group with a large Q-3 those which showed a Q wave with a value of 50 per cent or more of the maximum excursions of the QRS group, there are found to be twenty-two such records. Sixteen of these patients (73 per cent) suffered from the anginal syndrome, and of the other six patients all but one had a diagnosis which might well have involved coronary narrowing. These other diagnoses were: three with myocardial fibrosis and congestive failure, and one each with syphilitic aortitis, rheumatic aortic insufficiency and neurocirculatory asthenia. This large Q-3 is evidently closely associated with any pathologic changes that involve coronary narrowing, and it would seem that the larger the Q wave in relation to the voltage of QRS, the closer is this association.

Parkinson and Bedford⁴ noted the large Q-3 in a group of patients whom they considered to have had a thrombosis of a coronary branch. It occurred in nine, or 31 per cent, of the twenty-nine patients whose records they published, a figure that is comparable to the 27 per cent (eight times in thirty cases of anginal syndrome) which I found in a slightly different selection of cases. Three of their records showed a small Q-3, and two cases which at first showed a large Q-3 came to show a small one as time and healing progressed (figs. 18 and 19 in their article).

The change from a large to a small Q-3 was also observed in one of my cases (fig. 4). A boy, aged 9, had had two attacks of rheumatic cardiac involvement during the previous three years. He was not seriously ill with either of these, but the second attack lasted for nine months, was accompanied by mild chorea and left him with mitral insufficiency and slight cardiac enlargement. The first record, *A*, was taken five months after the end of the second attack, and the second, *B*, after a further interval of twenty months, during which he was well and gained weight and strength. These cases are of great interest because of their indication that a record with a small Q-3 may at times represent the healing of a process which might previously have given a record with a large Q-3. On the other hand, records with normal or left axis deviation and a small Q-3 are frequently obtained from hearts that are undoubtedly normal, so that such records cannot by any means be considered as having a pathologic significance.

Another fact has been observed that cannot be without significance in understanding the records here described. In a series of twenty-three cases of rheumatic pericarditis which were collected by Dr. Daniel Porte

4. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* **14**:195, 1928.

from the New York Hospital records, six cases have been found with records of this peculiar type with a large Q-3. It appears that there is something about the rheumatic invasion of the heart, perhaps especially about rheumatic pericarditis, that gives rise to a QRS group of this sort.

Certain other features related to this peculiarity of Q-3 have an important bearing on attempts to understand its meaning. A QRS in lead 3 like that seen in figure 3 *A* with a large R and small Q is a common feature of records from normal hearts, and especially of those showing right axis deviation of QRS. It occurred twenty-two times in the normal series of Lewis and Gilder, many of which indicated right axis deviation,

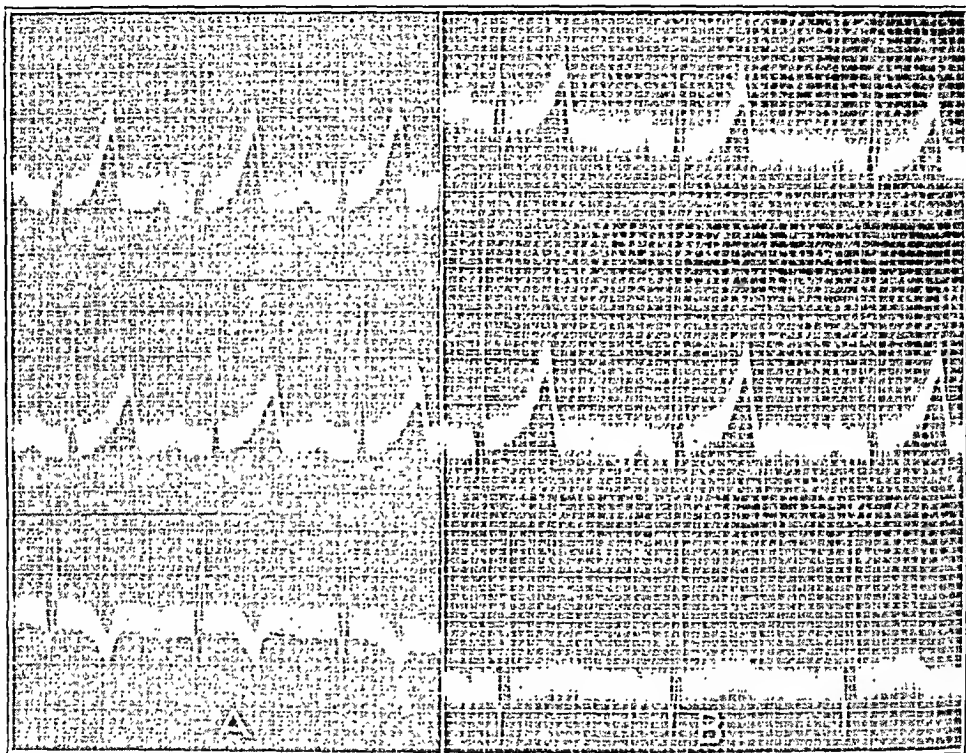


Fig. 4.—Two records of the same patient: *A*, large Q-3, more than 25 per cent of R-1; *B*, record taken eighteen months later showing a small Q-3, less than 25 per cent of R-2.

and twenty-nine times in a series of fifty of my records showing right axis deviation. This would suggest that Q-3 is related to the activity of the right ventricle. The Q wave of lead 3 has been related to the activity of the right ventricle by Lewis on other grounds.⁵

Lewis also demonstrated that when the ventricular systole starts in the right ventricle, as it does after section of the left branch of the A-V bundle, or with a right ventricular premature beat, the first portion of

5. Lewis, T.: The Spread of the Excitatory Process in the Vertebrate Heart, *Phil. Tr. Roy. Soc. London* 207:221 (March) 1916.

the QRS group is inscribed by electrical currents the successive units (vectors) of which rotate progressively in a clockwise direction.⁵ The QRS group of records obtained from hearts with preponderant hypertrophy of the right ventricle (curves with right axis deviation of QRS) also shows a progressive clockwise rotation of the successive electrical forces (vectors) of which it is composed.⁵ Curves of a contraction starting in the left ventricle, however, and curves with left axis deviation of QRS show a counter-clockwise rotation of the electrical vectors of QRS.

As has been noted, the records with a large Q-3 here under discussion show left axis deviation, as a rule, with R-1 larger than R-2, though in

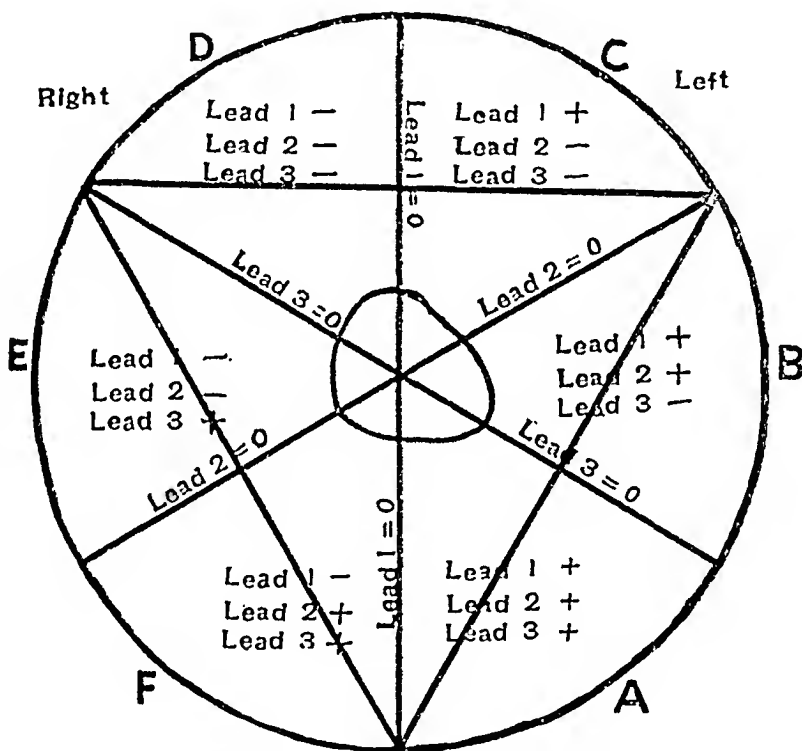


Fig. 5.—Diagram, showing direction of the deflections in the three leads resulting from vectors with various directions (after Pardee: Clinical Aspects of the Electrocardiogram).

some records the electrical axis is in the normal direction with R-2 larger than R-1 or R-3. When QRS shows left axis deviation, lead 3 does not have an R wave followed by an S, as is usual for records with left axis deviation. Instead of this, the downward deflection is a Q wave, followed by an R, and as a result the electrical currents (vectors) developed during the QRS group do not progress in a counter-clockwise direction as is usual for records with left axis deviation. The records with a large Q-3 are found to have a clockwise rotation of the vectors of QRS, no matter whether left axis deviation is present or the axis of QRS is in the normal direction. This will appear from the following.

If Q is present in all three leads the initial vectors of QRS will lie in sector D of figure 5, for the deflections will be lead 1—, lead 2—, lead 3—. Usually Q is found only in leads 2 and 3, in which case the initial deflection will be some portion of the R wave in lead 1, and some portion of Q in leads 2 and 3, so that the deflections will be lead 1 +, lead 2—, lead 3—, and the vectors will lie in sector C.

One comes now to a latter portion of the R in lead 1, approximately the peak. This will correspond approximately to the peak of the R wave in lead 2 and to a later portion of the Q wave in lead 3 or to an R wave in lead 3, according to the relative height of the R waves in lead 1 and in lead 2. If R-2 is greater than R-1, there must be a positive value in lead 3 which will lie in the R wave. If R-1 is greater than R-2, the corresponding value would be negative (downward) in lead 3 which will be a portion of the Q wave. If the deflections are lead 1 +, lead 2 +, lead 3—, the vector lies in sector B of the figure, or if lead 1 +, lead 2 +, lead 3 +, in sector A. This portion of the QRS group usually involves the peak of R-1 or of Q -3 and usually develops the largest voltage of the QRS group. In some records Q is found only in lead 3, so that the initial deflections are R in lead 1, R in lead 2, and Q in lead 3; the values are +, +, — and the vectors lie in sector B of the figure. In such records the initial deflections usually develop the largest voltage of QRS.

The last portion of QRS usually has an S in lead 1, less often an S in lead 2, and always an R in lead 3. The deflections accordingly are either — — + or — + +, and this places the vectors in sector E or F of the figure. Occasionally there is no S in lead 1 or lead 2, and such records have the last deflections upward (+) in each lead, so that the vectors lie in sector A. In records with a QRS of this type the largest deflection of QRS lies in this sector. It will be seen, then, that in the QRS group of records with a large Q -3 the currents may develop in various ways. The vectors may be first in sector B and then in F, or first in C, then in B or A and then in F or E, or first in B and then in F or E. Two things are always observed: (1) The direction of rotation of the vectors is clockwise, and (2) the vectors of the largest voltage of QRS (the electrical axis of QRS) will usually lie in sector B, though sometimes in sector A, indicating left axis deviation in the first case and normal direction of the electrical axis in the second. This clockwise rotation of the vectors suggests a predominance of the effect of the right ventricle during the spreading of the contraction, even though right axis deviation of QRS is not present.

The inversion of T-3 is another right ventricular effect. It is always present when the contraction starts in the right ventricle.⁵ With or without inversion of T-2 it is very common (25 per cent) in records showing

right axis deviation of QRS.⁶ The inversion of T-1 and T-2, on the other hand, is never found when the contraction starts in the right ventricle⁵ and is very rare (3 per cent) in records showing right axis deviation.⁶ In this series of thirty-three records with a large Q-3, twelve records (28 per cent) had an upward T in all leads, five records (12 per cent) showed an inversion of T-1, with or without T-2, and twenty-six records (60 per cent) showed an inversion of T-3 or of T-2 and T-3.

It must be significant that right ventricular effects are suggested by the clockwise rotation of the vectors of QRS in all of the records with a large Q-3, and that in two thirds of them the T wave is affected as with right ventricular premature beats and with preponderant hypertrophy of the right ventricle. It is suggested that these features indicate a predominance of the right ventricle during the spreading of the contraction in these hearts, in spite of their left or normal axis of QRS, and that the reason for this peculiarity may lie in a particular sort of damage to the left ventricular muscle. From the clinical studies shown in the table it appears that narrowing of a branch or branches of the left coronary system is the commonest causes of this left ventricular damage. The finding of a large Q-3 in patients with active rheumatic myocardial disease suggests disproportionate damage to the left ventricular muscle by the rheumatic process. In the patients with hypertension and cardiac arrhythmia there may possibly have been a complicating coronary arteriosclerosis affecting the myocardium of the left ventricle with the large Q-3 as its sole manifestation. The explanation of this feature in the records from the four supposedly normal hearts in this series lies possibly in an incorrect diagnosis of normal heart, for two of these hearts were shown to be definitely enlarged by the orthodiagraphic tracing. It is likely that a better understanding of the causes of this wave would afford an explanation that would apply to the normal hearts as well as to the abnormal ones. Possibly an occasional cause in normal hearts may lie in peculiar variations in the branching of the A-V bundle.

It is important to note the effect of deep inspiration on the waves of a QRS group of this type. Figure 6 shows lead 3 of four patients with this peculiar wave. In the upper three records forced inspiration was present at the left end and normal expiration at the right end. It will be observed that with inspiration the Q becomes smaller and the R larger, so the form shown could not be considered abnormal. Though the left axis deviation is abolished and Q-3 made smaller, yet clockwise rotation of the vectors of QRS still remains. In this connection also it is important to note that the case (accompanying table) with normal heart and pregnancy failed to show a large Q-3 in a record taken ten

6. Pardee, H. E. B.: *Clinical Aspects of the Electrocardiogram*, ed. 2, Paul B. Hoeber, Inc., 1928, pp. 42 and 53.

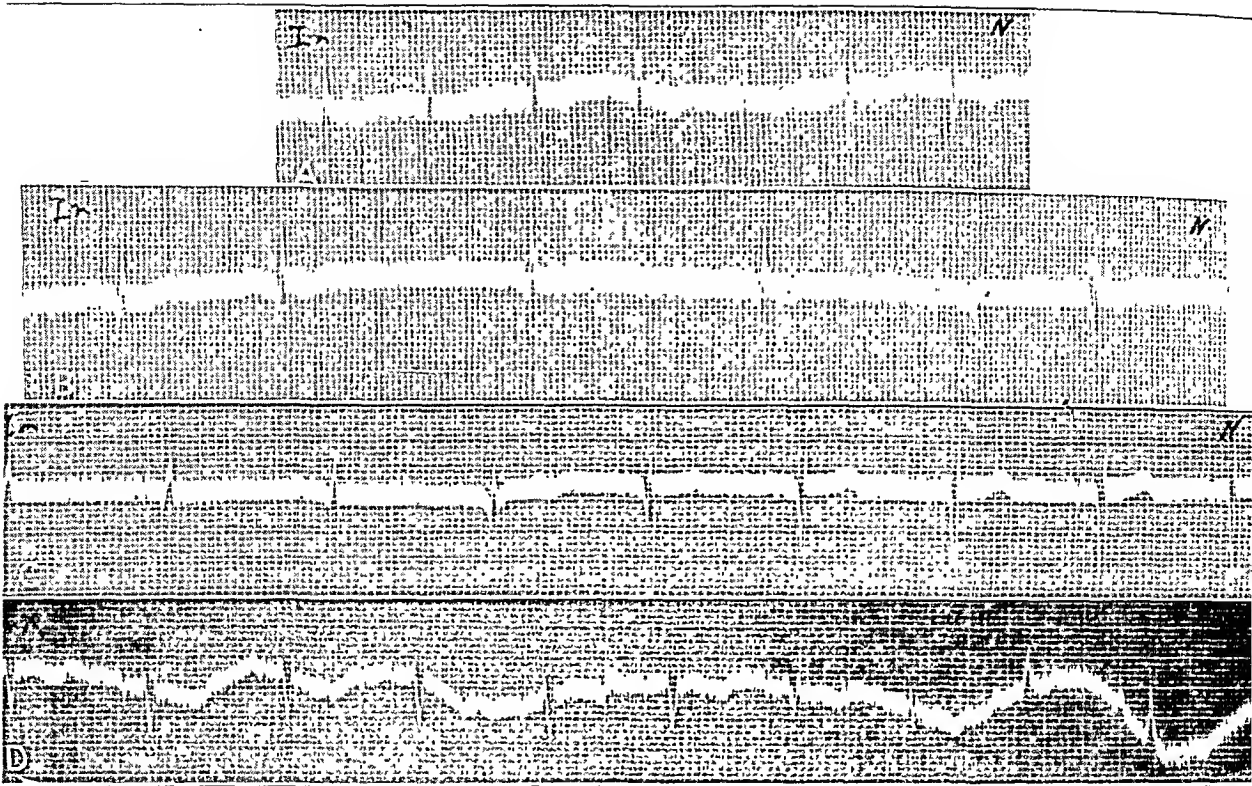


Fig. 6.—*A, B, C*, the third lead of three patients; full inspiration is present at the left, and normal expiration at the right; *D*, the third lead of the patient whose records appear in figure 7; forced expiration was present at the left, and forced inspiration at the right.

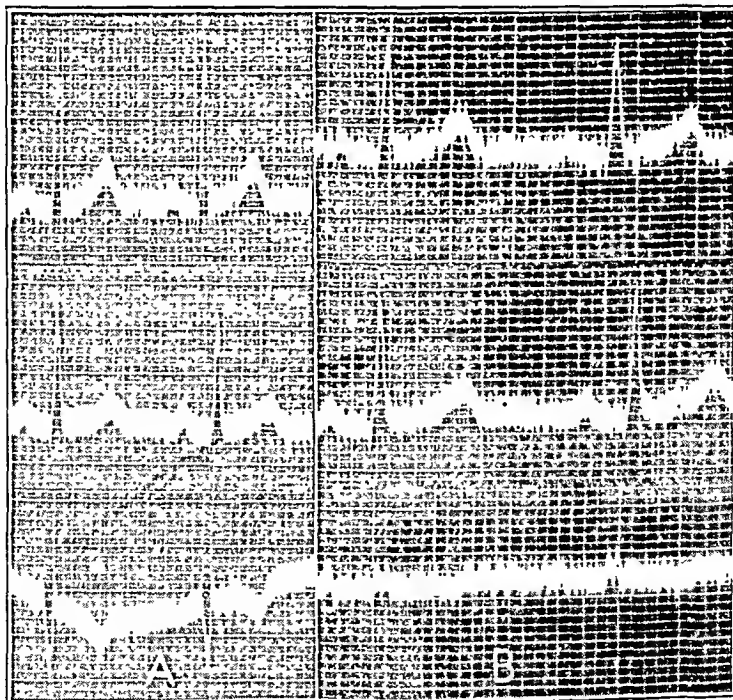


Fig. 7.—*A*, record with a large Q-3 obtained from a patient with a normal heart during the eighth month of pregnancy; *B*, record of the same patient eleven months after delivery.

months after delivery. Figure 7 shows the record taken during pregnancy which is included in this series, and also the record taken after delivery. The long strip, figure 6 *D*, is lead 3 of this patient taken on the last occasion, forced expiration being present at the left end of the record and full inspiration at its right end. The change in the QRS during the inspiratory process is striking, and illustrates well the importance of the position of the heart within the chest. The first heart cycle of this record shows a large Q and a small R much like the lead 3 of the record taken during pregnancy. The next five cycles show a QRS of the M type; the seventh cycle has a notched QRS; the eighth closely resembles that of lead 3 taken after delivery (fig. 7 *B*), while the last two cycles show nothing but an R wave—no downward deflection. Changes in the position of the heart and diaphragm are known to cause radical changes in QRS and these changes in position appear to bear some special relation to the finding of a large Q-3 in records from certain normal hearts. A high position of the diaphragm seems to favor the appearance of a large Q-3, while a low position is unfavorable. Each of the two patients in Cohn's normal series who showed a large Q-3 had hearts that were shown by roentgenograms to be more horizontal than the average.

SUMMARY

Attention is directed to the occurrence of records showing left axis deviation of QRS or a normal electrical axis, combined with a large Q wave in lead 3, one that is 25 per cent or more of the largest deflection of QRS in whichever lead this may occur.

The majority of such records are obtained from patients with the anginal syndrome, but certain patients with myocardial fibrosis and congestive failure, certain patients with rheumatic heart disease, especially with pericarditis, and a few with hypertension will give such records. Certain patients who have cardiac symptoms but no definite evidence of cardiac disease have been found to show this large Q-3, and rarely (twice in 277 cases) such records are obtained from apparently normal hearts.

These records show a clockwise rotation of the vectors of the QRS group, and frequently there is an inversion of T-3 or of T-2 and T-3. Both of these features depend on right ventricular activity, and it is suggested that the finding of a large Q-3 indicates disease of the left ventricle, so that the right ventricle predominates during the spreading of the contraction in spite of the left axis deviation or normal axis direction of QRS. The effect of diaphragmatic movements on the large Q-3 is noted, and it is suggested that the occasional finding of a large Q-3 in normal hearts may be due to an unusual distribution of the branches of the A-V bundle and that a high position of the diaphragm may be a contributory factor.

MODIFICATION OF THE DEXTROSE TOLERANCE TEST AS AN INDEX OF METABOLIC ACTIVITY OF THE LIVER *

T. L. ALTHAUSEN, M.D.

LEWIS GUNTHER, M.D.

JOHN B. LAGEN, M.D.

AND

WILLIAM J. KERR, M.D.

SAN FRANCISCO

Attempts to utilize disturbances of carbohydrate metabolism for a diagnosis of functional impairment of the liver are not new. But the levulose and galactose tolerance tests that are available do not give sufficiently uniform results to warrant their general adoption. The objections to these sugar tolerance tests as an indication of liver function are twofold. The first and real objection is that while sugar metabolism suffers in certain diseases of the liver, this fact is susceptible of consistent demonstration only by group averages. In individual cases of even proved diseases of the liver, the results of these tests frequently fall within the limits of normal and minimize their significance. The second objection is that other organs, such as the pancreas and the hypophysis, also play a prominent part in the metabolism of carbohydrates, and therefore any discovered abnormalities of such metabolism may not be due specifically to a deficiency of the liver.

The proposed method of testing the carbohydrate metabolism described in the following paragraphs was devised to overcome the first objection. The second objection is theoretically more difficult to overcome, but in practice with a suitable carbohydrate tolerance test at hand it should present no greater difficulties in the diagnosis of diseases of the liver than one encounters in the diagnosis of diabetes mellitus, in spite of the knowledge that other organs besides the pancreas are concerned with utilization of sugar.

The principle of the present test was evolved while we were carrying on metabolic studies on a patient having hemochromatosis with diabetes and cirrhosis of the liver, in whom fluctuations of great magnitude were observed in the blood sugar level following slight changes in the intake

* Submitted for publication, Feb. 14, 1930.

* From the Department of Medicine, University of California Medical School.

of carbohydrate or the dosage of insulin.¹ This extreme instability of the blood sugar level was ascribed to marked impairment of the glycogenetic and glycogenolytic functions of the liver, and the question arose as to whether or not a method could be found to bring out milder forms of a similar impairment in other patients suffering from hepatic disease. Such a method was found in a test whereby three functions of the liver are taxed at once, thus bringing out latent deficiencies which would escape detection if only one function were tested. This method will probably offer new possibilities in the functional study of other organs.

A review of the literature with this in mind, brought to our attention the work of Klein,² who observed unusually high and low blood sugar levels in patients with hepatic disease after simultaneous administration of dextrose and large amounts of water. He suggested that this might be used for functional testing of the liver. The downward fluctuation of the blood sugar level in these cases is accentuated even more by simultaneous administration of insulin.³

It may be mentioned here that as early as 1902, clinical disturbances of the intermediary water metabolism in hepatic disease were described and that at present the important rôle of the liver in the regulation of water metabolism is well established by numerous workers.⁴

METHOD

On the basis of this knowledge, a method was devised consisting of the administration of insulin, dextrose and water followed by observations of the blood sugar level over a period of three hours. The following schedule was found to answer our purpose and was adhered to in all reported cases: In the morning, with the patient fasting, a specimen of the blood was taken for sugar determination followed by an injection of 20 units of insulin. Twenty minutes later, 50 Gm. of dextrose dissolved in 500 cc. of water was given to the patient by mouth followed by

1. Althausen, T. L., and Kerr, W. J.: Hemochromatosis: A Report of Three Cases with Results of Insulin Therapy in One Case, *Endocrinology* **11**:377 (Oct.) 1927.

2. Klein, O., and Lang, E.: Ueber die Beeinflussung der alimentären Hyperglykämie bei Leberkranken durch Wasserbelastung, München. med. Wchnschr. **73**:187, 1926.

3. Klein, O.: Weitere Studien über Insulin und Wasseraushalt sowie über Insulinwirkung bei Leberkranken, *Med. Klin.* **21**:1116, 1925.

4. Molitor, H., and Pick, E. P.: Die Bedeutung der Leber für die Diurese, *Arch. f. exper. Path. u. Pharmacol.* **97**:317, 1923. Adler, A.: Der Einfluss der Leber auf die Wasserausscheidung, *Klin. Wchnschr.* **2**:1980, 1923. Saxl, P., and Donath, F.: Wasserhaushalt und reticuloendotheliales System, *Klin. Wchnschr.* **3**:1397, 1924.

1,000 cc. of water also administered by mouth. After this two samples of blood were taken at intervals of thirty minutes and two more at intervals of one hour. In cases in which insulin reactions developed during the test, the last sample of blood was taken at the time of the reaction regardless of schedule, and the patient was treated for hypoglycemia in the usual way. Previous to the test, all patients were kept on a general hospital diet for a period of at least several days.

The test has been applied to sixty-four patients with and without clinical evidence of hepatic disease. Only one of these patients experienced difficulty in taking 1.5 liters of fluids, and in no case did we meet with an insulin reaction of alarming severity.

RESULTS

In persons without evidence of hepatic disease, we observed blood sugar curves similar to that shown in the chart (solid line), which represents a composite curve of ten normal tests. It is characteristic of such curves that the blood sugar content rises during the first hour of the test and then gradually declines, until at the end of three hours it is again near the level maintained during fasting. The only difference between our composite curve and a normal blood sugar curve after the ingestion of 100 Gm. of dextrose is that in the former, the original level is reached in three hours instead of two. The same results, namely, delayed return of the blood sugar curve to normal, were obtained by Sweeney⁵ in hydrated dogs subjected to the dextrose tolerance test.

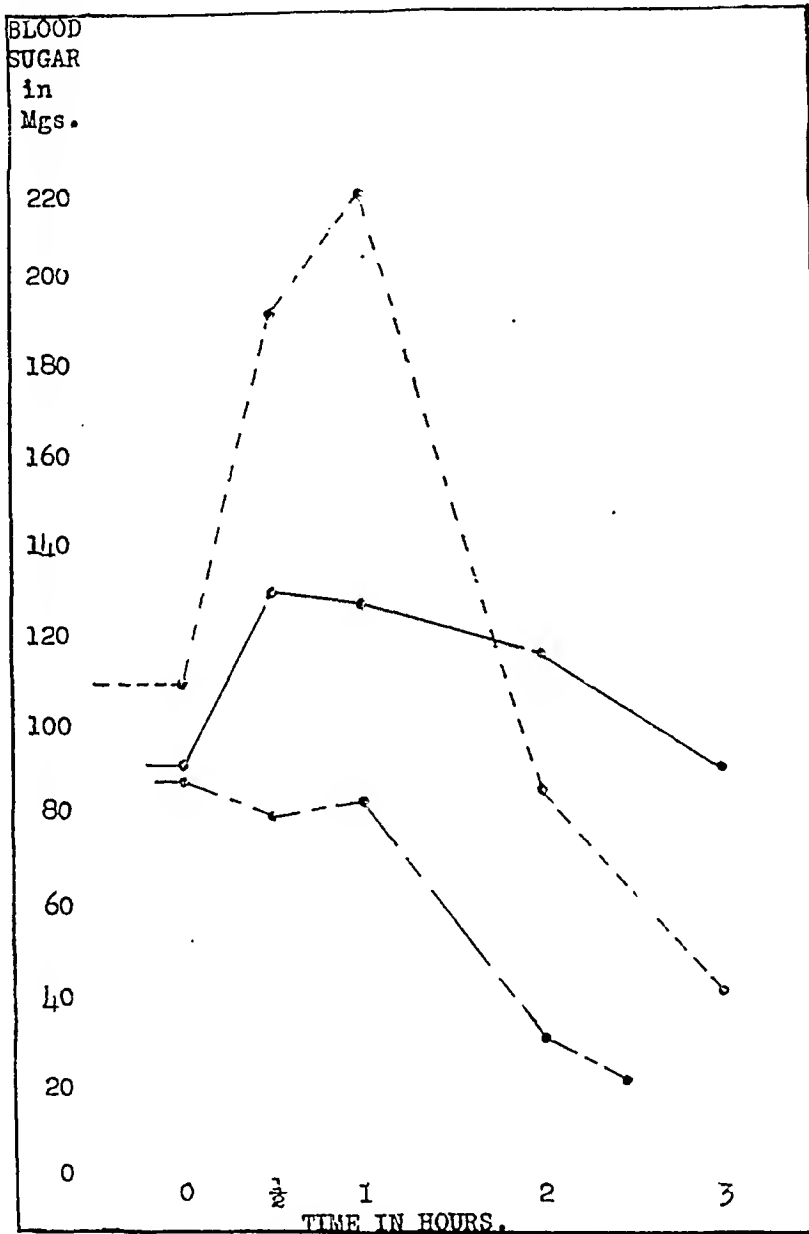
In patients with clinical evidence of hepatic insufficiency, blood sugar curves following our test were irregular, falling between the two extremes given in the same chart (broken lines). One of these curves shows marked hyperglycemia before the terminal hypoglycemia is reached and in the other there is an uninterrupted falling off of the blood sugar level during the entire duration of the test. However, all such abnormal curves have in common the eventual low blood sugar level, usually accompanied, as would be expected, by insulin reactions.

The conclusion from this was that, terminal hypoglycemia under the conditions of the test meant injury of the liver. The question immediately arose as to the dividing line between the normal and the abnormal. After clinical study of our cases and comparison with other liver function tests, principally the rose bengal dye excretion test, we decided to place it in the vicinity of 70 mg. of sugar per hundred cubic centimeters of blood. It is of interest that Hewlett⁶ also gave this figure as the lowest normal.

5. Sweeney, J. S.: Dietary Factors that Influence the Dextrose Tolerance Test, *Arch. Int. Med.* **40**:818 (Dec.) 1927.

6. Hewlett, A. W.: *Pathological Physiology of Internal Diseases*, ed. 2, New York, D. Appleton & Company, 1923, p. 270.

The average lowest blood sugar level in fifty-five positive modified dextrose tolerance tests was 50 mg. The individual readings ranged from 23 to 70 mg. but only ten of these patients had a minimum blood sugar level of over 55 mg. On the other hand, in ten negative tests the average lowest blood sugar was 95 mg., with variations between 73 and



Normal and two abnormal blood sugar curves following the modified dextrose tolerance test. The solid line represents an average of ten normal tests. The regularly broken line gives our most outspoken hyperhypoglycemic curve. The irregularly broken line traces the most marked simple hypoglycemic curve in this series.

122 mg., and only four cases reached a level below 98 mg. Such a wide zone between positive and negative results is considered in most cases one of the important advantages of the modified dextrose tolerance test.

The interpretation of differences between various types of abnormal blood sugar curves, aside from the final low blood sugar level, is not clear. We do not know whether these are expressions of hepatic insufficiency of various degrees, or whether we are dealing with impairment of the entire carbohydrate metabolism-regulating function of the liver in some cases and with dysfunction of glycogenolysis only in others. We are also unable to correlate these variations with any clinical entity involving the liver.

It is of interest that in positive cases the degree of hypoglycemia toward the end of the test is little influenced by the maximum height of the blood sugar curve, as the following figures will demonstrate: In cases in which the peak of the blood sugar curve was from 140 to 221

TABLE 1.—*Diseases of the Liver*

Diagnosis	Num- ber of Cases	Modified Dextrose Tolerance Test				Rose Bengal Test			
		Posi- tive	Nega- tive	Average in Mg.	Range of Readings in Mg.	Posi- tive	Nega- tive	Aver. at 16 Min. in %	Range of Readings in %
Portal cirrhosis.....	4	3	1*	47	41-55 (144)*	3	..	55	41-63
Toxic cirrhosis.....	5	1†	5	35	70-122 (52)†	4‡	..	54	33-84
Syphilitic cirrhosis.....	2	2	..	46	40 and 52	1	1§	..	65 and 0§
Probably early cirrhosis..	6	6	..	47	35-66	6	..	49	35-77
Metastatic carcinoma of the liver.....	5	5	..	52	40-60	4	..	56	45-70
Echinococcus cyst of the liver.....	2	2	..	45	39 and 50	2	..	48	35 and 63
Infectious jaundice.....	4	3	1#	57	48-69 (224)#	4	..	58	35-87
Arsphenamine jaundice...	2	2	..	49	31 and 67	2	..	62	35 and 85
Complete obstructive jaundice.....	1	1	23

* Patient also had diabetes with blood sugar of 157 mg. during fasting.

† During the acute stage; later it became negative.

‡ Deep icterus in one case precluded the rose bengal test.

§ Atypically negative, probably due to splenomegaly.

|| Deep icterus in one case precluded the rose bengal test.

Patient also had diabetes with blood sugar of 162 mg. during fasting.

|| Rose bengal test omitted due to deep jaundice.

mg., the average lowest blood sugar at the end of the test was 50.5 mg.; in cases in which the maximum blood sugar reached between 100 and 140 mg., it was 48.4 mg., and in cases in which the blood sugar curve at all times remained below 100 mg., it was 40.4 mg.

Diseases of the Liver.—Thirty-one cases of hepatic disease were studied with the results shown in table 1. It will be noticed at once that in all but one of the twelve cases of portal, syphilitic and suspected cirrhosis of the liver, the modified dextrose tolerance test gave positive results. The negative results in the single exception were due to an associated diabetes mellitus with a high blood sugar level at the beginning of the test. The significance of this will be taken up in a discussion on limitations of the present test. On the other hand, all five patients with toxic cirrhosis of the liver were proved to have normal carbohydrate metabolism during the chronic stage of their disease. One of these

patients did show positive results in the modified dextrose tolerance test, but only when seen during one of her acute attacks. These recurrent attacks in the course of toxic cirrhosis are, according to Mallory and others, in the nature of subacute yellow atrophy of the liver. The preservation of normal carbohydrate metabolism in this form of cirrhosis of the liver is explained by active regeneration of hepatic cells, which, however, in contrast to other types of cirrhosis, do not connect with bile channels and therefore are unable to partake in excretory processes.⁷

In seven patients with localized lesions of the liver due to metastatic carcinoma and to echinococcus cysts, the modified dextrose tolerance test gave uniformly positive results. Likewise, six of seven patients suffering from various types of jaundice had impaired carbohydrate metabolism

TABLE 2.—*Disease of the Hemopoietic and Lymphatic Systems*

Diagnosis	Number of Cases	Modified Dextrose Tolerance Test				Rose Bengal Test			
		Positive	Negative	Average in Mg.	Range of Readings in Mg.	Positive	Negative	Aver. at 16 Min. in %	Range of Readings in %
Myeloid leukemia (hepatomegaly in all but one case).....	4	4	..	52	42-65	3	1*	60	58-63 (5)*
Lymphoid leukemia with hepatomegaly.....	1	1	45	1	68
Pernicious anemia with large liver.....	1	1	41	1	39
Banti's disease with hepatomegaly.....	1	1	65	1	65
Hodgkin's disease with large liver.....	1	1	48	1	38
Splenomegaly (marked unexplained).....	1	1	47	..	1	..	30†
Polycythemia vera with hepatomegaly.....	1	1	33	..	1‡	..	20

* Atypically negative in patient with marked splenomegaly; only patient without enlarged liver.

† Upper limit of normal.

‡ Splenomegaly present.

regulation. The negative results in one case were brought about again by a complicating diabetes with high fasting sugar content of the blood.

Diseases of the Hemopoietic and Lymphatic Systems.—In all ten patients with various afflictions of the hemopoietic or lymphatic systems, the modified dextrose tolerance test detected abnormalities of carbohydrate metabolism (table 2). In eight of these cases, marked hepatomegaly was the chief reason for testing the function of the liver.

Miscellaneous Cases.—In this group shown in table 3 the modified dextrose tolerance test was positive in seven patients who had marked multiple chronic infections, such as pulmonary tuberculosis, gonorrheal prostatitis and chronic sinusitis in the same patient. The carbohydrate

7. The details of this process with presentation of pathologic material will be published shortly by the senior author under the title, "Functional Aspects of Regenerated Hepatic Tissue."

metabolism-regulating function of the liver was also found to be impaired in two cases of arsenical dermatitis and in one case of chronic interstitial nephritis with ascites and pleural and pericardial effusions.

The test was negative in two cases of arteriosclerosis with hypertension, and in one case each of carcinoma of the urethra and uncomplicated chronic interstitial nephritis.

Limitations of the Test.—Theoretically, one could expect any abnormalities of the carbohydrate or water metabolism other than those attributed to the liver to invalidate the modified dextrose tolerance test. With

TABLE 3.—*Miscellaneous Cases*

Diagnosis	Number of Cases	Modified Dextrose Tolerance Test				Rose Bengal Test			
		Positive	Negative	Average in Mg.	Range of Readings in Mg.	Positive	Negative	Aver. at 16 Min. in %	Range of Readings in %
Multiple chronic infections.....	7	7	..	42	35-60	5	1	37	10-55
Arsenic dermatitis.....	2	2	..	39	31 and 47	2	..	57	40 and 74
Chronic nephritis.....	2	1*	1	..	33 and 98	2	..	67	65 and 68
Arteriosclerosis with hypertension.....	2	..	2	107	106 and 108	1†	1	..	20 and 80
Carcinoma of urethra....	1	..	1	..	109	1	40

* Patient had fluid in all serous cavities.

† Patient had chronic passive congestion.

TABLE 4.—*Conditions which Theoretically Should Interfere with Estimations of Carbohydrate Metabolism*

Diagnosis	Number of Cases	Modified Dextrose Tolerance Test				Rose Bengal Test			
		Positive	Negative	Average in Mg.	Range of Readings in Mg.	Positive	Negative	Aver. at 16 Min. in %	Range of Readings in %
Diabetes mellitus.....	2	..	2*	..	73 and 291	1	1	..	20 and 80
Thyrototoxicosis.....	4	4†	..	50	42-61	2	..	68	48 and 87
Myasthenia gravis.....	1	1‡	57	..	1	..	15
Diabetes insipidus.....	1	1	43	..	1	..	30§

* Patient with positive rose bengal test had a blood sugar level of 328 mg. during fasting.

† Patient also had diabetes, but blood sugar during fasting was 133 mg.

‡ Patient also had diabetes, but blood sugar during fasting was 101 mg.

§ Upper limit of normal.

this in mind we studied two common and two rare conditions involving such metabolic disturbances (table 4).

Five patients with and without evidence of hepatic disease whose conditions gave a typical diabetic curve in the ordinary dextrose tolerance test were subjected to our carbohydrate liver function test. In three of these, the blood sugar level during fasting was high at the beginning of the test. All three cases gave negative results in the face of marked rose bengal dye retention, and there was well marked clinical evidence of hepatic disease in two cases. On the other hand, of two patients with diabetes and a nearly normal blood sugar level during fasting at the

beginning of the test, one had normal and the other impaired carbohydrate metabolism regulation. In both cases there was agreement with the rose bengal test. The obvious conclusion is that diabetes per se does not interfere with the accuracy of the modified dextrose tolerance test, provided there is no marked hyperglycemia at the beginning of the test.

Four patients with marked thyroid hyperplasia with basal metabolic rates between 46 and 85 per cent plus were also subjected to the carbohydrate function test for the purpose of testing the possibility of abnormally low blood sugar levels, being due to increased oxidation of dextrose in this disease. All four patients gave positive results to our test, and although in both cases in which it was done the rose bengal test confirmed the presence of hepatic damage, it still remains to be shown that negative results to the modified dextrose tolerance test can take place in the presence of a high basal metabolism. Indirect proof in favor of this is found in the fact that, in a considerable proportion of such cases, the increased metabolism associated with hyperthyroidism does not prevent hyperglycemia with galactosuria following galactose tolerance tests. Functional impairment of the liver in severe thyrotoxicosis is probably accounted for by focal necrosis of this organ sometimes seen at postmortem examination.

In one case of myasthenia gravis, with diminished dextrose tolerance, the modified dextrose tolerance test showed positive results and the rose bengal test negative results. Disturbances of carbohydrate metabolism, according to Gibson and his associates,⁸ are the rule in cases of myasthenia gravis. In addition, this condition is a disease of muscles which, as shown by Engels,⁹ play an important rôle in the intermediate water metabolism. Thus we are dealing with an entity in which all metabolic functions involved in our test are affected and combine to invalidate its results.

One patient with diabetes insipidus also showed definite impairment of carbohydrate metabolism regulation, but in this case, the rose bengal test being just at the upper limit of normal made it impossible to say without study of more cases whether we were dealing with real injury to the liver or not. Theoretically, it is quite probable that the disturbances of water metabolism characteristic of diabetes insipidus, especially the frequently present unusual delay in the elimination of extra quantities of liquids, would interfere with the accuracy of the test.

8. Gibson, R. B.; Martin, F. T., and Van Rennselaer Buell, M.: A Metabolic Study of Progressive Pseudohypertrophic Muscular Dystrophy and Other Muscular Atrophies, *Arch. Int. Med.* **29**:82 (Jan.) 1922.

9. Engels, W.: Die Bedeutung der Gewebe als Wasserdepots, *Arch. f. exper. Path. u. Pharmakol.* **51**:346, 1903.

COMPARISON OF RESULTS OBTAINED WITH THE MODIFIED DEXTROSE TOLERANCE AND THE ROSE BENGAL TESTS

In all but seven of our cases the rose bengal dye liver function test was performed for comparison. In three of these cases, the presence of deep icterus made it superfluous because in any case of jaundice dye elimination is impaired at least in proportion to the depth of jaundice. We realize that since the rose bengal test is an excretion test, while the modified dextrose tolerance test is a metabolic one, agreement between the two tests cannot be expected in all instances. On the other hand, a confirmation of the results of the modified dextrose tolerance test, which is in the experimental stage, by an established test like that of rose bengal dye elimination was of great value in this work, especially in cases in which, from the clinical point of view, there were no definite reasons to suspect damage to the liver.

In comparing the results of these two liver function tests, we must exclude cases of: (1) toxic cirrhosis (in which the very contrast between the results of the two tests constitutes a valuable diagnostic aid); (2) diabetes mellitus with high blood sugar level during fasting; (3) myasthenia gravis and diabetes insipidus, and (4) splenomegaly which may give false negative results with the rose bengal test, apparently because of overdevelopment of the reticulo-endothelial system of the spleen which takes an important part in the disposal of dyes used for the functional testing of the liver.¹⁰

It exceeded our most optimistic expectations to find that after eliminating cases in which inaccuracy of one or the other of the two tests can be predicted *a priori*, there were only four cases in which the results of these liver function tests did not agree. In three of these with diagnoses of chronic interstitial nephritis, arteriosclerosis with hypertension, and carcinoma of the urethra, the modified dextrose tolerance test gave negative results. In the fourth, a case of multiple chronic infections, the rose bengal elimination was normal. Translated into percentages, this means 91 per cent agreement between the two tests as to presence or absence of hepatic damage in all our cases. Moreover, in patients with diseases of the liver and of the hemopoietic and lymphatic organs, comprising forty-one cases, there was complete agreement in the outcome of the two tests.

PHYSIOLOGIC BASIS OF THE MODIFIED DEXTROSE TOLERANCE TEST

Attempts at explanation of the mechanism involved in the production of hypoglycemia under the conditions of our test in cases of hepatic disease, at the present stage of our knowledge, must of necessity carry

10. Schellong: Funktionsprüfung der Leber oder des reticuloendothelialen Systems mit Farbstoffen, Med. Klin. 22:1711, 1926.

us into the field of speculation. However, we believe that we are in the possession of sufficient evidence to point out a probable theory.

This theory has as its basis the assumption suggested by Klein³ that in diseases of the liver there is slowing of metabolic activity on the part of its cells. Insulin which is given at the beginning of the test apparently promotes oxidation of sugar in the tissues and at the same time tends to inhibit glycolysis, in this way bringing about lowering of the blood sugar level. In addition, the ingestion of a large amount of water, which may or may not gain premature admission to the general blood stream in cases of hepatic injury, diminishes the blood sugar content even further. A parallel to this is described by Epstein,¹¹ in cases in which diabetic hyperglycemia is masked by an increase in blood volume. In normal persons the dextrose ingested during the test seems to be polymerized to glycogen and in turn released as dextrose with sufficient rapidity to counteract impending hypoglycemia, whereas in patients with hepatic disease this process is sufficiently slowed to permit of reaching abnormally low blood sugar levels.

The part played by the glycogen reserve of the liver at the time of the test is of great importance. The connection between the glycogen content of the liver and its functional activity is well known. To mention only two examples, a high glycogen content of this organ brings about faster assimilation of carbohydrates¹² and also increases the detoxifying power of the liver.¹³ We know that in some diseases of the liver its glycogen content is markedly depleted,¹⁴ and therefore the possibility that this may be responsible for hypoglycemia under the conditions of the test must be considered.

On the other hand, without denying that the glycogen content of the liver is playing some part in the outcome of the modified dextrose tolerance test, it is safe to assert that it is not the only factor involved because, by giving insulin and water without the dextrose we can produce hypoglycemia in normal persons in whom the addition of 50 Gm. of dextrose is capable of preventing an undue lowering of the blood sugar level.

Since this question is important not only from the diagnostic but also from the therapeutic point of view, because the answer to it would throw

11. Epstein, A. A.: The Influence of Renal Function on Hyperglycemia and Glycosuria in Diabetes Mellitus, *Am. J. M. Sc.* **154**:103, 1917.

12. Staub, H.: Untersuchungen über den Zuckerstoffwechsel des Menschen, *Ztschr. f. klin. Med.* **93**:89, 1922.

13. Opie, E. L., and Alford, L. B.: Diet and the Hepatic Lesions of Chloroform, Phosphorus or Alcohol, *J. Exper. Med.* **21**:1, 1915.

14. Ravdin, I. S.: Some Aspects of Carbohydrate Metabolism in Hepatic Disease, *J. A. M. A.* **93**:1193 (Oct. 19) 1929. Umber, F.: Akute und subacute Leberatrophie, *Klin. Wchnschr.* **1**:1585, 1922.

more light on the combined dextrose and insulin treatment of diseases of the liver, we have plans under way to test this combined treatment by animal experimentation.

Other possible theories which were given by Klein,¹⁵ who did much fundamental work in this field, seem less probable to the authors but deserve mention. One of these, based on the work of Lesser,¹⁶ accounts for the hypoglycemia by an undue hydration of the liver with consequent swelling resulting in a separation of the diastatic ferment from the glycogen within the individual hepatic cells.

Another theory advanced by Klein is founded on the researches of Häusler and Loewi,¹⁷ who claimed to have isolated a substance "glykamine" which is antagonistic to insulin. In health, these two substances are said to be in equilibrium, but in diseases of the liver the dextrose releasing "glykamine" is reduced in amount with a consequent tendency toward latent hypoglycemia, which is brought out under conditions of the modified dextrose tolerance test.

Before conclusion of this paper, it seems timely to remove any remaining doubts that a function of the liver is on trial in the modified tolerance dextrose test. We know that by our method glycogenolysis on the part of the liver is being tested, in the first place, because Simpson and Macleod¹⁸ showed that liver glycogen is the only source of blood sugar; in the second place, because Villa¹⁹ found at the height of insulin hypoglycemia the lowest sugar concentration to be not in the peripheral blood but in that of the hepatic veins. We also have indications that glycogenesis is involved in this test because hypoglycemia is produced in normal persons if the administration of dextrose is omitted from the test.

The question may be asked whether the diet preceding the modified dextrose tolerance test can influence its outcome, since Sweeney⁵ demonstrated that antecedent diets of an extreme nature definitely alter the carbohydrate tolerance of persons. The answer to this is given by later

15. Klein, O., and Holzer, H.: Beobachtungen über Insulinhypoglykämie, Insulinschock und Insulinleukocytose beim Menschen, *Ztschr. f. klin. Med.* **106**:360, 1927.

16. Lesser, E. J.: Die Wechselbeziehung zwischen Glykogen und Traubenzucker in der Leberzelle und ihre Bedeutung für die Lehre vom Pankreasdiabetes, *Ergb. d. inn. Med. u. Kinderh.* **16**:279, 1918.

17. Häusler, H., and Loewi, O.: Untersuchungen über Diabetes und Insulinwirkung, *Arch. f. exper. Pathol. u. Pharmacol.* **123**:56, 1927.

18. Simpson, W. W., and Macleod, J. J. R.: The Immediate Products of Post-Mortem Glycogenolysis in Mammalian Muscle and Liver, *J. Physiol.* **64**:255 (Dec.) 1927.

19. Villa, L.: Die Rolle der Leber während der Insulinhypoglykämie, *Klin. Wchnschr.* **4**:551, 1925.

work of the same author²⁰ showing that dextrose tolerance was not appreciably influenced when antecedent standardized diets were compared with uncontrolled general diets. As already mentioned, all tests in the present series were carried out on the stomach during fasting, after the patients had been on a general hospital diet for at least several days.

SUMMARY

Evidence is presented to show the value of the modified dextrose tolerance test as a metabolic liver function test.

The test possesses the following advantages: (*a*) It is simple and requires no special equipment. (*b*) It is harmless to the patient. (*c*) Unlike the levulose and galactose tolerance tests, it is reliable not only in disease groups but also in individual cases. (*d*) It brings out latent functional impairment of the liver and permits one to follow the progress of the disease. (*e*) It checks well with the results of the rose bengal test. (*f*) As a metabolic test, its results are probably independent of biliary obstruction. (*g*) In combination with a dye excretion test, it offers valuable diagnostic aid in toxic cirrhosis of the liver.

The chief limitation of the modified dextrose tolerance test is its inaccuracy in cases of diabetes mellitus with marked morning hyperglycemia.

20. Sweeney, J. S.: A Comparison of the Effects of General Diets and of Standardized Diets on Tolerance for Dextrose, *Arch. Int. Med.* **42**:872 (Dec.) 1928.

RENAL DAMAGE FOLLOWING ADMINISTRATION OF MERBAPHEN (NOVASUROL)

REPORT OF NINE CASES *

DOUGLAS H. SPRUNT, M.D.

Sterling Research Fellow

NEW HAVEN, CONN.

Merbaphen (novasurol) is accepted as a useful diuretic in many cases of edema due to congestive heart failure. Attention has been called by Marvin¹ and others to its immediate toxic effect in some cases. That there may be damage to the renal epithelium for as long as four weeks after the last injection of merbaphen was mentioned by Redlich.² He reported an instance of damage to the tubular epithelium of the kidney in a patient with tuberculosis who died four weeks after an injection of 1 cc. of the drug. Saxl³ immediately claimed that the damage to the kidney could not have been due to the merbaphen because of the period of time that had elapsed since its use. He said, moreover, that even if the mercury were responsible for the lesions, it was given under conditions that clearly contraindicated its use. The question of the toxicity of merbaphen raised by Redlich and Marvin has engaged my interest because of certain experiences which I have had.

Among 741 necropsies performed between Jan. 1, 1926, and Dec. 31, 1928, nine instances were found in which the patients received merbaphen during the clinical course of their illness. In three of these cases, extensive necrosis of the renal epithelium was observed. Attention is drawn to the fact that in case 1 merbaphen was given under circumstances adverse to its use, while in cases 2 and 8, conditions which may be considered as counterindications were also present. In the case reports given herein only the points in the clinical history and necropsy observations which seem particularly relevant are summarized.

REPORT OF CASES

CASE 1.—*Clinical History*.—M. S., a negress, aged 53, a cook, had dizziness, blurring of vision, dyspnea and edema of the ankles of one year's duration. Dur-

* Submitted for publication, Feb. 28, 1930.

* From the Department of Pathology, Yale University School of Medicine.

1. Marvin, H. M.: Merbaphen (Novasurol) as a Diuretic in Congestive Heart Failure, J. A. M. A. **87**:1016 (Sept. 25) 1926.

2. Redlich, Fritz: Letale Quicksilberintoxikation nach einmaliger Novasurol-injektion, Wien. klin. Wchnschr. **38**:350, 1925.

3. Saxl, Paul: Letale Quicksilberintoxikation nach einmaliger Novasurolinjektion, Wien. klin. Wchnschr. **38**:437, 1925.

ing this time she was under constant medical attention, and her blood pressure was known to have been elevated. Her condition improved whenever she was confined to bed. On admission examination showed the temperature to be 98.4 F., the pulse rate 120 per minute, the respirations 22 per minute and the blood pressure 153 systolic and 110 diastolic. The patient was dyspneic and edematous. The heart was enlarged. A systolic murmur, heard over the precordium, was loudest in the apical region. A diastolic murmur was audible over the lower part of the sternum. The second aortic sound was accentuated. Moist, crackling râles were present over the bases of both lungs. The abdomen was distended, and the liver was enlarged. An ophthalmoscopic examination showed the right disk to be partially obliterated by a large, white patch. An electrocardiogram revealed a left bundle branch block. The specific gravity of the urine varied between 1.010 and 1.014. During the first week in the hospital, with the patient on digitalis therapy, the output of urine was less than one third of the fluid intake. Six days after admission, the patient was given 1 cc. of merbaphen, and three days later an additional 2 cc. The second dose produced a slight diuresis. Repeated doses of theophylline, however, produced a diuresis which resulted in the loss of 22 pounds (10 Kg.) in four days. Following this treatment the condition of the patient gradually improved until four days before death, when she complained of pain in the right side and began to cough up a bloody sputum. Dulness was found over the base of the right lung, and numerous hemorrhages were seen in the retina. The temperature rose to 101 F., the leukocyte count to 25,000 cells. Following the rise in temperature, an additional dose of merbaphen resulted in bloody diarrhea. The patient grew rapidly worse, and died thirty-one days after admission to the hospital and three days after the last administration of merbaphen.

The clinical diagnosis was arteriosclerosis with hypertension and heart disease, congestive heart failure, intraventricular block and auriculoventricular block, acute mercury and digitalis poisoning and infarcts of the lungs.

Pathologic Report.—At necropsy, performed twenty-two hours after death, the kidneys were found not to be enlarged and to present only a few arteriosclerotic scars. They were bright red and were slightly swollen. Nothing else of note was observed on gross examination. Microscopically, the kidney showed the architecture to be well preserved and well stained, except for the convoluted tubules. The cytoplasm of these cells was extremely granular, and the nuclei were either pyknotic or missing. No calcification of these cells and no nuclei undergoing mitotic division were observed. The mucosa of the small intestine was present throughout. The mucosa of the large intestine was covered with a dull, greenish-black, opaque membrane. When the membrane was removed, the mucosa was found to be pierced by numerous indented ulcers, between which the mucosa appeared bright red and hemorrhagic. Microscopic preparations of the ileum showed only a few small areas of necrosis in the mucosa, while preparations of the colon showed the mucosa to be necrotic in some places and to contain hemorrhagic areas in others. The submucosa and muscularis showed evidence of edema and a diffuse polymorphonuclear leukocytic infiltration.

The complete anatomic diagnosis was:

Primary: (a) Necrosis and calcification of the myocardium; cardiac hypertrophy and dilatation; chronic passive congestion of the viscera; general anasarca; mural cardiac ventricular and auricular thrombi; pulmonary and splenic infarcts; necrotizing colitis,⁴ and epithelial necrosis of the kidney.⁴

4. Mercury poisoning from merbaphen.

tubules contained a large amount of pink-staining, homogeneous material. The nuclei of some of these cells were vesicular. The complete anatomic diagnosis was:

Primary: (a) Calcification and stenosis of the aortic valve; cardiac hypertrophy; passive congestion of the viscera; edema of the extremities; hydrothorax (bilateral); mural thrombi of the left auricular appendage, auricle and left ventricle, with focal myocardial fibrosis; acute aortic endocarditis; thrombus in the abdominal aorta, and thrombi of the pulmonary vessels with pulmonary infarct.

Subsidiary: Left varicocele.

CASE 5.—*Clinical History*.—N. D., a white woman, aged 51, had always been subject to nose bleed. She first noticed swelling of the ankles, palpitation and shortness of breath on exertion seven years before death. These symptoms became gradually worse, and two and one-half years later she was admitted to the New Haven Hospital where the diagnosis of hemangiomas of the skin and mucous membranes, rheumatic heart disease, mitral stenosis and regurgitation, aortic and tricuspid regurgitation and congestive heart failure was made. The patient remained in the hospital for about a month and was discharged greatly improved. For two years she remained fairly well. During the last two and one-half years of her life she was admitted to the hospital three times because of edema. During this time she was given three 1 cc. doses and eight 2 cc. doses of merbaphen, all of which resulted in a marked diuresis. The last dose was given seven weeks prior to death. Death occurred after an infection of the upper respiratory tract. The specific gravity of the urine varied between 1.010 and 1.024.

The clinical diagnosis was hemangiomas of the skin and mucous membranes; rheumatic heart disease; mitral stenosis and regurgitation; aortic and tricuspid regurgitation; congestive heart failure, and auricular fibrillation.

Pathologic Report.—Necropsy, performed eighteen hours after death, showed large, pale, slightly swollen kidneys. Numerous cortical scars were seen. One kidney contained a small abscess.

Microscopic preparations showed the kidneys to be well stained and the architecture well preserved. The cells lining the convoluted tubules were low, their cytoplasm was granular and the nuclei were deep-staining. One section showed the abscess described in the gross.

The complete anatomic diagnosis was:

Primary: (a) Healed mitral, tricuspid and aortic endocarditis; cardiac hypertrophy and dilatation (involving particularly the right ventricle); pulmonary emphysema; pulmonary fibrosis; passive congestion of the viscera, and fibrosis of the liver; ascites.

Subsidiary: Focal pneumonia; scars of the kidney; abscess of the kidney (right); adenoma of the thyroid, and fibromas of the uterus.

CASE 6.—*Clinical History*.—T. B., a farm laborer, aged 53, had had dyspnea on exertion and orthopnea for nine months. These symptoms improved with rest, but he had been unable to work during that period. The orthopnea finally became so marked that he was sent to the hospital. On admission, examination showed the temperature to be 97.5 F., respirations 20 per minute, the radial pulse rate 40, the apical pulse rate 80 and the blood pressure 145 systolic and 110 diastolic. The patient was markedly cyanotic, and there was some edema of the extremities. He improved with rest in bed and digitalis therapy but continued to have some edema. He was given three 2 cc. doses of merbaphen seventy-seven, eleven and six days before death. An excellent diuretic effect was obtained each time. The specific gravity of the urine varied between 1.012 and 1.018.

tory tests were essentially negative. The condition of the patient grew progressively worse, edema gradually increased and death occurred eighteen days after the patient's last admission to the hospital and thirty-five days after the last dose of merbaphen.

The clinical diagnosis was arteriosclerotic heart disease with congestive heart failure and paroxysmal auricular tachycardia.

Pathologic Report.—Necropsy, performed three hours after death, showed the kidneys to be approximately normal in size. They were dark red and slightly swollen but showed nothing else of note grossly. Microscopic preparations of the kidney showed numerous vacuoles in the glomerular tufts. The remainder of the kidney, except for the cells forming the convoluted tubules, was well stained and preserved. The cytoplasm of the convoluted tubules was pale pink and granular. Many of the cells had desquamated into the lumen of the tubules. The nuclei of these cells were either missing or pyknotic, although there were several mitotic figures seen as evidence of regeneration. The intestines showed nothing of note either grossly or microscopically.

The complete anatomic diagnosis was:

Primary: (a) Fibrosis of the myocardium; cardiac hypertrophy and dilatation, chronic passive congestion of the viscera; ascites and anasarca; pulmonary atelectasis (left), and pulmonary emphysema (right).

Subsidiary: Epithelial necrosis of the kidney; 4 fibrous adhesions of the pleura (right); fibrous adhesions of the cecum to the abdominal wall, and cyst of the kidney (left).

CASE 4.—*Clinical History.*—S. N., a white man, aged 52, a baker, was first admitted to the New Haven Hospital with the complaint of dyspnea and swelling of the feet. The symptoms began two years before admission, when he was forced to give up work. His condition improved with rest in bed, and he was discharged from the hospital. Six months later he was readmitted, following an infection of the upper respiratory tract, complaining again of edema and dyspnea. After rest and digitalis therapy, he was discharged as improved. He discontinued the use of digitalis at home, and was readmitted four months after his second discharge from the hospital. At this time the temperature was 98.6 F., the respirations were 32 per minute, the pulse rate 80 per minute and the blood pressure 122 systolic and 105 diastolic. The patient was edematous. The liver extended to the umbilicus. The heart was enlarged, and bubbling râles were heard over the bases of both lungs. The amount of phenolsulphonphthalein excreted in two hours and ten minutes was 65 per cent, and the specific gravity of the urine varied between 1.016 and 1.030. In an attempt to relieve the edema, 1.2 cc. of merbaphen was given, and three, nine and twenty-three days later, additional doses of 2 cc. each were administered. All of these resulted in an excellent diuresis. The patient's general condition grew steadily worse, and death occurred on the forty-fourth day after his last admission and twenty days after the last dose of merbaphen.

The clinical diagnosis was arteriosclerotic heart disease, aortic stenosis and congestive heart failure.

Pathologic Report.—Necropsy, performed two hours after death, showed the kidneys to be dark red and slightly swollen but of about average size. Microscopic preparations of the kidney showed the tissue to be well stained and preserved except for the cells forming the convoluted tubules. The cytoplasm of these cells was slightly granular. The cells in some instances were swollen to such an extent that the lumen was completely obliterated, while in other places the lumina of the

months previously edema and dyspnea had appeared. Because of the poor condition of the patient, no further history was obtainable. On admission the temperature was 98 F., the pulse rate was 95 per minute, the respirations 30 and the blood pressure 205 systolic and 125 diastolic. Physical examination showed the patient to be dyspneic and orthopneic. The heart was slightly enlarged, and the extremities and abdomen were markedly edematous. The edge of the liver was felt at the level of the umbilicus. Her course in the hospital was steadily retrogressive. One cubic centimeter of merbaphen was given four days before death, with no diuretic effect. The specific gravity of the urine varied between 1.007 and 1.012. The blood nonprotein nitrogen was 89 mg. per hundred cubic centimeters.

The clinical diagnosis was arteriosclerosis with hypertension; heart and kidney disease; congestive heart failure, and syphilis (on the basis of a positive Wassermann test).

Pathologic Report.—Necropsy, performed two and one-half hours after death, showed small kidneys which were swollen and pale. The renal capsule was almost completely separated from the kidney by fluid. The cortical striations were not made out.

Microscopic preparations showed the typical picture of a chronic nephritis. The cells lining the convoluted tubules were well preserved, the cytoplasm being only slightly granular. The nuclei were vesicular.

The complete anatomic diagnosis was:

Primary: (a) Scars of the kidneys; hyalinized glomeruli; dilatation of the tubules; hypertrophy and atrophy of the renal epithelium; glomerular adhesions; cardiac hypertrophy and dilatation; fibrosis of the myocardium; congestion of the viscera; anasarca; focal lesions of the pancreas and liver, and acute diffuse nephritis.

Subsidiary: Thrombosis of the right ovarian vein; chronic cholecystitis and pericholangitis, and duodenal ulcers.

CASE 9.—*Clinical History.*—F. R., a white man, aged 55, had had an anginal attack, lasting for fifteen minutes, three months before admission. Three weeks after this he had a similar attack, which was relieved only by morphine. Since then he had remained in bed. On admission to the hospital the temperature was 100 F., the pulse rate was 110 per minute, the respirations were 40 and the blood pressure 100 systolic and 90 diastolic. The patient was dyspneic and orthopneic. There were edema of the legs, ascites and an enlarged liver and heart. He did not improve with hospital care. Death occurred suddenly on the eighth day, apparently from occlusion of the coronary artery. He received 1 cc. of merbaphen the day before death. The specific gravity of the urine varied between 1.013 and 1.015.

The clinical diagnosis was arteriosclerosis with heart disease; infarct of heart, and congestive heart failure.

Pathologic Report.—Necropsy, performed five hours after death, showed that the kidneys were not enlarged and that the architecture was well preserved.

Microscopic preparations of the kidneys showed the architecture to be well preserved and the tissue to be well stained. The cells lining the convoluted tubules had extremely ragged edges, and many had sloughed off into the lumen. The cytoplasm was granular, and most of the nuclei were vesicular, although a few were deeply stained.

The complete anatomic diagnosis was:

Primary: (a) Arteriosclerosis, involving especially the coronary arteries; cardiac hypertrophy and dilatation; chronic passive congestion of the liver; mural thrombi in the ventricles; pulmonary infarcts (bilateral), and anasarca.

About 30 per cent of the phenolsulphonphthalein injected intramuscularly was excreted in two hours and ten minutes. Death occurred following a cerebral embolus.

The clinical diagnosis was arteriosclerosis with hypertension and heart disease; auricular fibrillation; paroxysmal tachycardia; congestive heart failure; infarct of heart, and cerebral embolus.

Pathologic Report.—A necropsy, performed twenty-seven hours after death, failed to verify the diagnosis of cerebral embolus. The kidneys were not enlarged. There were a few arteriosclerotic scars.

Microscopic preparations of the kidneys showed the architecture to be well preserved and the tissues well stained. The cells lining the convoluted tubules were low, the cytoplasm was granular, and the nuclei were vesicular.

The complete anatomic diagnosis was:

Primary: (a) Arteriosclerosis involving especially the coronary arteries; fibrosis of the myocardium; cardiac hypertrophy and dilatation; mural cardiac thrombi; organized pericarditis; ascites, and pulmonary infarcts.

Subsidiary: Apical pulmonary scars, and pleural adhesions.

CASE 7.—*Clinical History.*—Mrs. E. R., a white woman, aged 70, had some dyspnea on exertion about three weeks before admission to the hospital. Following this she became orthopneic, and edema of the ankles developed. On admission to the hospital her temperature was 100.2 F., the pulse rate was 104 per minute, the respirations 42 and the blood pressure 114 systolic and 72 diastolic. On physical examination the heart was found to be slightly enlarged, and the liver was felt below the costal margin. After admission her course was steadily retrogressive. A large amount of fluid developed in the left side of the chest, and had to be removed by tapping on several occasions. The last of these, when the patient was practically dying, resulted in a pneumothorax. Death occurred a few hours later. Five-tenths cubic centimeters of merbaphen was given twenty-five days before death and 1 cc. nineteen days before death. Neither dose produced any diuretic effect. The specific gravity of the urine varied between 1.014 and 1.022. The phenolsulphonphthalein excretion was 20 per cent in two hours and ten minutes.

The clinical diagnosis was arteriosclerosis with hypertension and heart disease; congestive heart failure, and pneumothorax.

Pathologic Report.—Necropsy, performed one and one-half hours after death, showed that the kidneys were not enlarged. The architecture in the gross was not distorted.

Microscopic preparations of the kidneys showed the architecture to be well preserved and the tissue well stained. The cells lining the convoluted tubules were high, and the lumen was small. The cytoplasm was slightly granular, and the nuclei were vesicular.

The complete anatomic diagnosis was:

Primary: (a) Senility; passive congestion of the viscera; hydrothorax (bilateral); pulmonary atelectasis (bilateral); subcutaneous edema; thrombosis of uterine veins; emboli in pulmonary arterioles; fibrinous pleurisy (left), and acute hepatitis.

Subsidiary: Apical pulmonary scars (bilateral); carcinoma metastases to bronchial lymph nodes and lungs, and fibrous pleural adhesions (bilateral).

CASE 8.—*Clinical History.*—E. G., a colored woman, aged 33, was brought to the hospital after dilatation and curettage of the uterus following an abortion. Four

TRANSFUSION FROM A GROUP II (A) DONOR TO A GROUP III (B) RECIPIENT WITH- OUT FATAL RESULT*

LYMAN BURNHAM, M.D.

NEW YORK

This case is reported not only because the transfusion of a group II (A) blood to a group III (B) recipient has been almost universally accompanied by severe reaction or death, but also because serologic study of the present case has shown why the usual fatal result did not take place.

REPORT OF A CASE

Mrs. M. H., aged 35, colored, weighing only 85 pounds (38.6 Kg.), was hospitalized for a pelvic operation. Her chief complaint was lower abdominal pain of three months' duration, especially on the right side. Because of a secondary anemia of 55 per cent hemoglobin with 3,400,000 red blood cells, a preoperative transfusion was deemed advisable. The patient's blood, with the use of the usual microscopic method of grouping, was found to belong to group III (B). Her husband's blood was grouped by the same method and appeared to be that of a universal donor; that is, it belonged to the Jansky group I (O). Cross-matching of his cells versus the patient's serum appeared to be satisfactory.

The transfusion was started with the Scannell method. With the idea of preventing, if possible, the headache or dizziness that not infrequently accompanies transfusions, the blood was transferred to the patient considerably more slowly than usual. After from 40 to 60 cc. had been given, the patient began to cough occasionally and complained of some oppression in the chest and slight dizziness. The pulse remained of good quality, the rate being constantly around 90, and the patient looked well. The transfusion was continued very slowly until the patient complained of pain in the lumbar region of the back, when it was immediately stopped, this being at 200 cc. After from five to ten minutes these symptoms entirely disappeared, the patient appeared well, and the transfusion was continued slowly. When 400 cc. had been given, the transfusion was stopped entirely because of the recurrence of occasional coughing and slight oppression in the chest. These symptoms, however, did not persist, and there was no recurrence of the pain in the back. As the patient left the room to return to the ward, she complained of slight headache but nothing else; the pulse rate was still 90 and the pulse was of good quality; the blood pressure was 126 systolic and 85 diastolic, which was essentially the same as before the transfusion. Immediately after the transfusion the temperature was 99.2 F., the pulse rate 90 and the respirations 24; two hours later, the temperature was 101, the pulse rate 94 and the respirations 20. This was the only temperature reaction that occurred. At the end of six hours the headache had entirely disappeared. The following day

* Submitted for publication, Jan. 10, 1930.

* From the Clinic of the Woman's Hospital in the State of New York, and the Division of Immunology, Department of Bacteriology and Immunology, Cornell University Medical College.

COMMENT

Merbaphen was given in three (1, 2 and 8) of the nine cases reported under conditions which are either known to be adverse to its use or might be so considered (fever, tuberculosis and chronic nephritis). In two of these cases (1 and 2) necrosis of the renal epithelium was found at necropsy. In case 8 no such damage could be found. Renal damage occurred in one (case 3) of the six remaining cases in which no known counterindications were present.

That it is impossible to obtain any correlation between the amount of merbaphen given and the renal damage which occurred is shown clearly in the accompanying table.

If case 1, in which the mercury was given by mistake after a rise in temperature, is ruled out, only two of eight cases remain in which

Tabulation of Clinical and Pathologic Observations

Case	No. of Doses	Total Amount Administered, Gm.	Time Between First Dose and Death	Time Between Last Dose and Death	Possible Counterindications	Diuresis	Damage to Renal Epithelium
1	3	4 to 5	25 days	3 days	Fever	+	++
2	2	3	32 days	30 days	Tuberculosis	+++	+
3	3	4.75	45 days	35 days	0	+	+
4	4	7.2	44 days	20 days	0	++	0
5	11	19	2½ years	49 days	0	+++	0
6	3	6	77 days	6 days	0	++	0
7	2	1.5	25 days	19 days	0	0	0
8	1	1	4 days	4 days	Nephritis	0	0
9	1	1	1 day	1 day	0	—	0

there was any anatomic damage to the kidney. It would appear, therefore, from this small series that the therapeutic use of merbaphen to produce diuresis is justifiable as a last resort.

SUMMARY

The clinical and necropsy reports of nine cases in which the patients received therapeutic intravenous injections of merbaphen are given. In one instance, the drug was given in the presence of a condition (fever) which is known to be adverse to its use. In two cases complications (tuberculosis and chronic nephritis) were present which may be considered as counterindications. One of these showed damage to the renal epithelium, and the other did not. Six of the nine cases showed no change, and the suggestion is made that the use of merbaphen is probably justifiable.

rapid massive clumping of the cells. This result was surprising in view of the demonstrated presence of unagglutinated donor's corpuscles in the recipient's blood. The paradox was explained in the following experiment. The same constituents were used but were kept at body temperature both before and after the mixture was made. Examination of this mixture on a warmed slide showed no agglutination until the slide began to cool, when complete agglutination took place. Both this agglutination on the slide and that which occurred when the mixture in the test tube was allowed to cool were resolved on rewarming.

The foregoing experiments show that the patient's serum contained no specific agglutinins active at body temperature, but only a powerful property of agglutinating the donor's cells at room temperature or at a still lower temperature. In view of the well known fact that cold agglutinins are usually not group-specific, that is, they act on the blood corpuscles of all groups, it was necessary to determine whether the strong cold agglutination exhibited by the patient's serum was due to the presence of such nonspecific cold agglutinins, or whether, as is rarely the case, the agglutination was caused by the group-specific α which was capable of acting only at temperatures lower than 37 C.

This question was answered by testing the patient's serum against a number of blood specimens of the different groups: twenty-four of group I (O), twenty-four of group II (A), six of group III (B) and four of group IV (AB). In no instance was any clumping observed of group I or group III cells, and in every case the group II and group IV cells were strongly agglutinated at room temperature. None of the three blood specimens of group II tested at body temperature showed agglutination at this temperature. These tests identify the agglutinin as the group-specific α acting only in the cold. No similar instance has been found in the literature, although the unanalyzed case of Jervell may have been of the same nature.

Landsteiner and Levine² succeeded in demonstrating, along with the common iso-agglutinin, the existence of a fraction of the α iso-agglutinin which was incapable of clumping group II (A) cells at body temperature. In these experiments the cold α was accompanied by the usual α acting at body temperature. In a later paper,³ a group A serum is described in which the β iso-agglutinin clumped B cells distinctly at room temperature but very weakly or not at all, depending on the blood cells, at body temperature.

2. Landsteiner, K., and Levine, Philip: On the Cold Agglutinins in Human Serum, *J. Immunol.* **12**:452, 1926.

3. Landsteiner, K., and Levine, Philip: On Isoagglutinin Reactions of Human Blood Other than Those Defining the Blood Groups, *J. Immunol.* **17**:23, 1929.

the patient felt well; the blood showed 70 per cent hemoglobin with 3,850,000 red blood cells, and the urine was free from albumin, sugar and blood cells.

On the second day following the transfusion a right salpingo-oophorectomy and appendectomy was done, an adnexal mass from 2½ to 3 inches in diameter and an adherent, injected appendix being removed. The pathologic diagnosis was ovarian abscess, chronic salpingitis and chronic appendicitis, chiefly peri-appendicitis. The patient made an uneventful recovery, was allowed out of bed on the twelfth day, and was discharged on the eighteenth day after the operation.

Because of the immediate symptoms of reaction, it was thought advisable to check the grouping of the donor's blood. This was done by the same examiner, with the same method and with the same specimens of test serums. This time the blood of the donor was found to belong to a clearcut group II (A) instead of to the universal donor group, as was previously thought. This was checked by others, as was also the recipient's grouping. The mistake made in the first grouping and cross-matching of the donor's cells must have been due to the use of a very dilute suspension of cells, together with failure to stir or agitate sufficiently the mixtures of widely separated donor's cells and test serums. In the hope of finding an explanation for the remarkably mild character of the symptoms, the following further serologic study was carried out.

Specimens of blood were obtained from the recipient on the third and sixth days after the transfusion, and designated specimens 1 and 2, respectively. The results of the grouping with the usual test serums were different with the two specimens. When tested with group III serum (anti-A), specimen 1 showed a few large clumps in the midst of a great preponderance of unagglutinated corpuscles; the mixture with group II serum (anti-B) showed massive clumping of most of the cells with, however, a small proportion of cells lying singly and flat. The similar mixtures with specimen 2 showed no clumps in the test with group III (anti-A) serum and no flat-lying single cells in the test with group II (anti-B) serum. The tests with specimen 2 definitely identify the recipient as a group III individual, and the tests with specimen 1 demonstrate the presence of the donor's group II cells in small proportion in the recipient's blood. This method of detecting the presence of agglutinable transfused corpuscles has been used before by Jervell¹ in instances of transfusion of agglutinable corpuscles in an infant lacking both iso-agglutinins and agglutinable substances, and also in an adult under circumstances similar to the present case.

When the serum of specimen 1 was mixed on the slide with a 1:20 suspension of the donor's corpuscles at room temperature, there was a

1. Jervell, F.: Untersuchungen über die Lebensdauer der transfundierten roten Blutkörperche beim Menschen, *Acta path. et microbiol. Scandinav.* **1**:155, 1924.

PARATHYROID TUMOR AND CHANGES OF THE BONES*

I. SNAPPER, M.D.

AMSTERDAM, HOLLAND

For some years, views regarding the origin and treatment of certain diseases of the skeleton have been expanded and improved. The following observations on a man aged 56, who had been bedridden for several years and whose condition had been diagnosed as osteomalacia, will serve in this connection.¹ The violent pain which the patient suffered defied all methods of treatment. He had given up all hope of recovery, and had come to the conclusion that he had an incurable disease. His only desire was that some chair or other apparatus could be constructed in which he would be able to rest without too much pain.

REPORT OF CASE

The patient was married and had a healthy wife and a healthy grown son. The somewhat complicated anamnesis showed that the patient had been well until 1922, when for the first time he noticed stiffness in his legs. In 1924 he fell to the pavement, hurting his knees, which became swollen and had to be aspirated. After having been in bed for two months he tried to get up, but could walk only with difficulty with the aid of two canes. He had continual pain in his legs, for which he was operated on in 1925. An operation for fractured patella was performed. After the operation, walking became even more difficult; the pain increased to such an extent that in 1927 another surgeon removed the iron wire with which the patella was held together in each knee. The tendon of the quadriceps muscle was sewn at the kneecap, but this afforded no relief. Since 1927 the patient had been unable to walk. By degrees his body became so tender to touch that it was an almost unbearable torture for him to have his bed made, and nursing was thus almost impossible. A spontaneous fracture of the right thigh-bone which occurred in January, 1929, when the patient was being carefully shifted in bed, further complicated his condition.

It must be emphasized that in 1925 a swelling developed on the top of the right foot; this gradually increased in size. The patient, who formerly had been extraordinarily strong and able to lift and push heavy weights, now grew weaker and weaker as the severe pains impaired his appetite and his sleep. He became emaciated and nervous, although he did not suffer from palpitation or perspiration. He had no cough, and his bowels moved regularly.

Even without roentgen examination, the diagnosis of osteomalacia or an analogous disease had to be considered, as in a few years the man had diminished in size; his back had become curved like a bow, and his thorax compressed. On the other hand, the lower thoracic aperture was dilated and nearly reached the

* Submitted for publication, Jan. 6, 1930.

1. Snapper: *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **41**:183, 1929; *Nederl. tijdschr. v. geneesk.* **2**:47, 1929.

The serum of the patient (specimen 1) was examined for group-specific hemolysin for group II (A) corpuscles with and without the addition of the donor's serum. The protocol of this test is seen in the table which shows that group-specific hemolysin was absent.

The experiments explain the fortunate outcome of the transfusion. One may surmise that the mild symptoms observed during the transfusion were due to some cooling of the transfused blood sufficient to cause a mild temporary agglutination. In the accessible literature on transfusions I found only one instance of the transfusion of incompatible blood without death. This was reported by Jervell,¹ who transfused 600 cc. of group I (O) blood and then 600 cc. of group II (A) blood into a group III (B) recipient. He mentioned no immediate symptoms but noted urobilinuria and general icterus. No serologic study of this case was made.

Test for Hemolysin in Serums of Recipient and Donor

Five per cent suspension of donor's cells.....cc.	0.2	0.2	0.2	0.2	0.2	0.2
Donor's serum	0.2	0.0	0.2	0.2	0.05	0.025
Patient's serum	0.0	0.2	0.2	0.1	0.05	0.025
Resulting hemolysis after 1 hour at 37 C.	0	0	0	0	0	0

The tests described were repeated in the presence of Philip Levine, Ella F. Grove and A. F. Coca, the results being confirmed.

SUMMARY

A full transfusion (400 cc. into a recipient weighing but 85 pounds) of group II (A) blood into a group III (B) recipient was accidentally performed, with only slight symptoms: coughing, oppression in the chest, slight dizziness and pain in the lumbar regions.

The incompatible transfused blood remained in the circulation of the recipient from three to five days.

The absence of serious consequences was shown to be due to the fact that all of the group-specific iso-agglutinin α in the recipient's serum was entirely incapable of clumping the group II (A) cells of the donor at body temperature, although it clumped these cells vigorously at room temperature.

case, therefore, in which the patient was a man aged 56, pseudo-osteomalacia seems more probable. From time to time similar decalcifications of large parts of the skeleton are met with in cases of dissemination of malignant metastases in the bones. This possibility received serious consideration in the present case, but a primary tumor was not found.

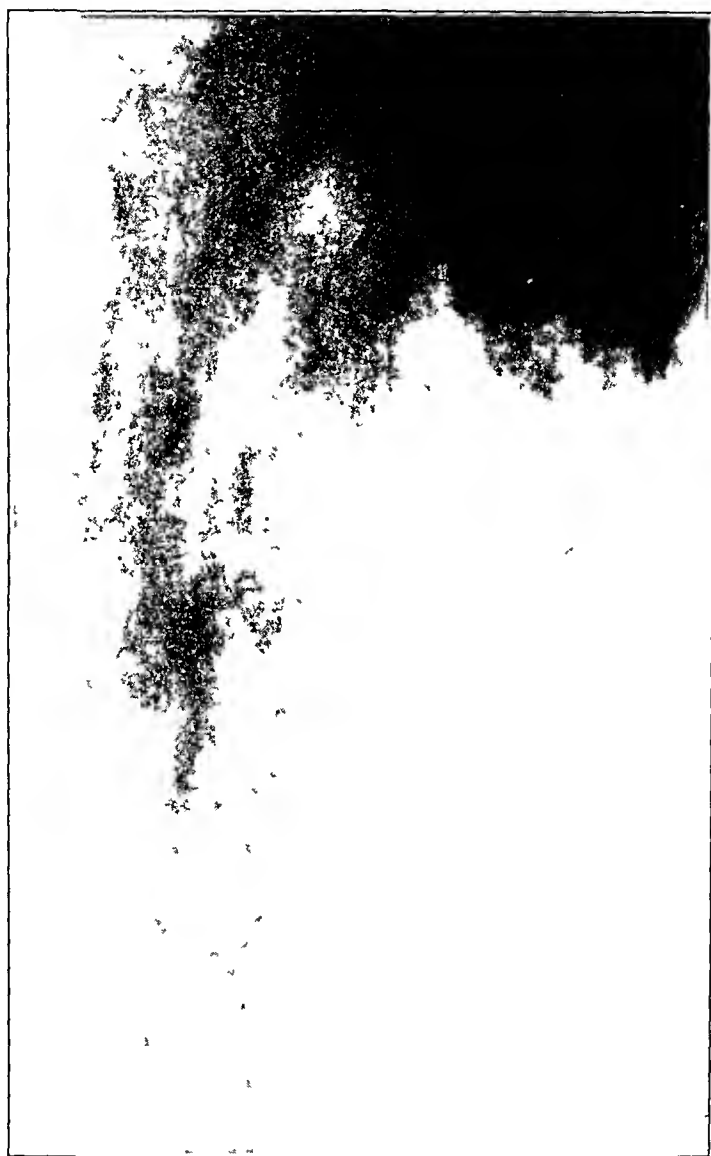


Fig. 2.—Femur before operation.

Later, during a more extensive examination of the patient, I stumbled on the fact that the blood serum contained an abnormally high amount of calcium. While, as a rule, the serum calcium of man is stable and fluctuates only between 9 and 12 mg. per hundred cubic centimeters of serum, unusually high calcium contents were found on four different occasions in the serum of the patient, viz., 19, 21.4, 22.8 and once even

upper border of the pelvis. The thighs were bent, and the feet lay in outward rotation. The thorax and the legs especially were extremely tender on pressure. On account of this enforced restriction in movement, the general examination was especially difficult. The heart and lungs, peripheral and central nervous system appeared normal, so far as they could be examined. Nothing abnormal was found in the abdominal organs. There was, however, extensive pitting edema of the legs, and a great number of leukocytes were present in the urine. The blood pressure was normal; the blood picture showed no abnormal cells; the Wassermann test was negative.

In September, 1928, a roentgen examination had shown extensive osteomalacic changes of the bones (Dr. Heilbron). The spine, pelvis and thighs were totally decalcified. The pelvis, for example, had become quite transparent; the natural

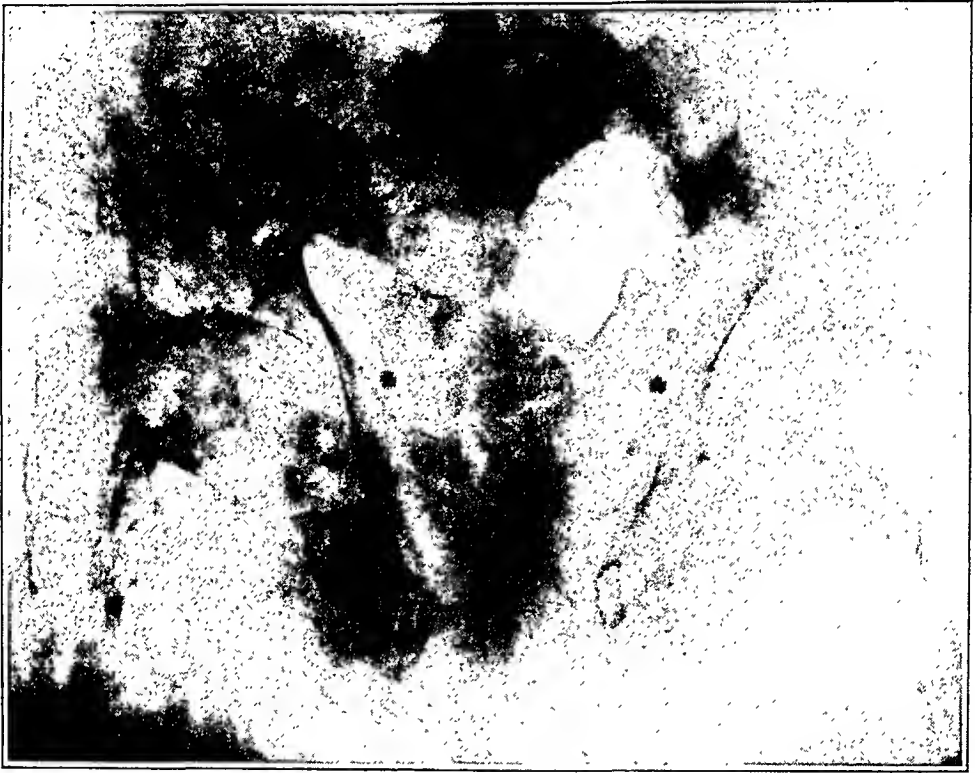


Fig. 1.—Pelvis before operation.

compression had brought about the typical form of wedge-shaped osteomalacic pelvis. The decalcification was less clearly pronounced in the arms, lower part of the legs, hands and feet. A nonconsolidated fracture was found on the right thigh bone. Although in a great part of the skeleton a marked decalcification existed, which in many respects reminded one of osteomalacia, the definite diagnosis of true osteomalacia seemed doubtful.

Osteomalacia, strictly speaking, is a disease which is characterized by decalcification of the bones, and it occurs especially during pregnancy. In children and in male adults extensive decalcification can also be observed. It is, however, inadvisable to consider these as cases of true osteomalacia, because most of these patients are suffering from osteomalacic end-stages of other diseases of the bones. In the present

bone is replaced by uncalcified osteoid tissue; finally decalcification is so extensive that the clinical symptoms may be identical with those of osteomalacia. True puerperal osteomalacia, however, may be distinguished anatomically from this pseudo-osteomalacic end-stage of osteitis fibrosa generalisata.²

It must be mentioned that there is much histologic resemblance between Recklinghausen's disease and the well known osteitis deformans Paget with its increase in the size of the scalp and in the thickening of the compacta of the long shaft bones. However, in agreement with the fact that the clinical picture of Recklinghausen's disease and that of Paget's disease are quite different, it must be noted that in Recklinghausen's disease an adenoma of a parathyroid is frequently observed, whereas in Paget's disease this tumor is hardly ever found.

Until a short time ago there was a difference of opinion with regard to the question of whether the tumor of the parathyroid was the cause or the result of the changes in the bones. Erdheim³ defended the opinion that primarily disease of the bones was present. The large quantities of calcium that are released by the degeneration of the skeleton make such great demands on the organs of the calcium metabolism (in this case, the parathyroids) that a compensatory hypertrophy of these glands results. This explanation, however, can hardly be brought forward in face of the fact that in osteitis fibrosa, as a rule, only one of the parathyroids is hypertrophied, while the others remain normal. Yet there are important arguments in favor of Erdheim's conception. Klemperer's observation, in particular, in which he noted a parathyroid tumor in a case of generalized carcinosis of the bone after mammary carcinoma, must be mentioned. In this case the decalcification through carcinosis seems to have been primary, whereas the tumor of the parathyroid was secondary. There are arguments, however, which point to the fact that Klemperer's⁴ observation probably is an exception to the rule, and that in most cases of osteitis fibrosa generalisata the tumor of the parathyroid must be considered as the cause of the disease of the bone. Günther⁵ also defended this opinion on the basis of anatomic observations.

This view found important support in a further analysis of the action of parathyroid extract-Collip. Injection of this substance causes increase of the calcium content of the serum in man and animals and

2. These facts are based on detailed reports in the discussion of the Deutsche Pathologische Gesellschaft in Freiburg, 1926.

3. Erdheim: Beitr. z. path. Anat. u. z. allg. Path. **33**:214, 1903; Frankfurt. Ztschr. f. Path. **7**:175, 1911.

4. Klemperer: Surg. Gynec. Obst. **36**: 11, 1923.

5. Günther: Frankfurt. Ztschr. f. Path. **28**:319, 1922.

in the calcium content of the skeleton was always observed after operation. Taking all these observations into account, it is highly probable that the parathyroid tumor is the cause of the osteitis fibrosa generalisata.

In the present case it was essential, therefore, to consider the possibility of a tumor of a parathyroid. It had to be borne in mind, however, that only osteomalacic changes were found, while nothing was known of osteitis fibrosa generalisata. Although parathyroid tumors may



Fig. 3.—Osteitis fibrosa cystica of the second metatarsal (taken in 1925 by Dr. Morlet, Antwerp)

be found at times in osteomalacia, these tumors are observed as a general rule in cases of osteitis fibrosa generalisata. Fortunately the patient had had roentgenograms taken in Antwerp in 1925 for the swelling on the right foot, as previously described. Dr. Morlet of Antwerp put them at my disposal. It appeared from these that a real osteitis fibrosa cystica of the second metatarsal of the right foot existed in 1925; they also showed an accumulation of cysts in the fossa glenoidalis of the scapula. The disease originated, therefore, as a real osteitis fibrosa cystica generalisata. The deduction could therefore be made that the condition was

also an increase of calcium output in the urine. Collip proved that this hypercalcemia is caused by the fact that parathyroid extract increases calcium absorption from the skeleton. If the injections are continued long enough, the skeleton loses so much calcium that spontaneous fractures may occur. One must consider, further, that not only Recklinghausen's disease but the continuous supply of parathyroid extract is accompanied by hypercalcemia, increased calcium secretion in the urine and spontaneous fractures. It is therefore probable that by increased production of parathyroid hormone the parathyroid tumor found in Recklinghausen's disease causes the greatest number of the symptoms of this illness.

Mandl, a surgeon from Vienna, has accepted this conception. Until a few years ago, Viennese scientists, especially, took interest in the problem of the occurrence of parathyroid tumors in cases of osteitis fibrosa generalisata and analogous diseases. On account of Erdheim's investigations, this question was repeatedly a subject of discussion at scientific meetings in Vienna. In 1915, during one of these discussions, Schlagenhauser raised the question as to whether one could not try to extirpate the tumor of the parathyroid in cases of osteitis fibrosa generalisata. Maresch supported this suggestion, but it was ten years before Mandl actually performed this operation (1925).⁶ For several years, on account of a generalized osteitis fibrosa, Mandl's patient, aged 38, had been able to walk only with the greatest difficulty and with the assistance of crutches; during the last months prior to the operation, he was bedridden on account of terrible pain. After the operation, which consisted of the removal of the parathyroid tumor, the patient gradually grew better. Although roentgenograms showed little improvement in the calcium content of the skeleton, the patient recovered sufficiently to work again like a man in an ordinary state of health.

Two years later Gold,⁷ also in Vienna, successfully operated on a second patient. In 1929, analogous cases were observed by Du Bois,^{7a} Barr⁸ and Wilder.⁹ In these American cases, also, clinical recovery from Recklinghausen's disease was obtained by operations on the parathyroid.¹⁰ In the American cases a roentgenologic improvement

6. Mandl: Arch. f. klin. Chir. **143**:1, 1926.

7. Gold: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **41**:63, 1928; Klin. Wchnschr., 1929, p. 2247.

7a. Hannon, R. R.; Shorr, E.; McClellan, W. S., and Du Bois, E. F.: J. Clin. Investigation **8**:215, 1930.

8. Barr, D. P.; Bulger, H. A., and Dixon, H. H.: Hyperparathyroidism, J. A. M. A. **92**:951 (March 23) 1929.

9. Wilder: Endocrinology **13**:231, 1929.

10. Boyd, J. D.; Milgram, J. E., and Stearns, G.: Clinical Hyperparathyroidism, J. A. M. A. **93**:684 (Aug. 31) 1929. Hunter, D.: Proc. Roy. Soc. Med. **23**:27, 1929.

the skeleton had been influenced favorably. The two less favorable symptoms were: (1) an obvious exophthalmos, probably caused by manipulation of the thyroid, an excessive amount of thyroid hormone having been pressed into the circulation during the operation; this symptom could be observed for only two days, after which it gradually disappeared; (2) the secretion of urine appeared to be disturbed. While at least 2 liters of urine was secreted daily before the operation, only 800 cc. was secreted on the day of the operation, and on the day after the operation, in spite of ample liquid supply, only 150 cc. This oliguria was especially unpleasant in this case, because the patient had severe pyuria and damaged kidneys. Even before the operation, with rest in bed and limited nourishment the nonprotein nitrogen of his blood was 31 mg. per hundred cubic centimeters.

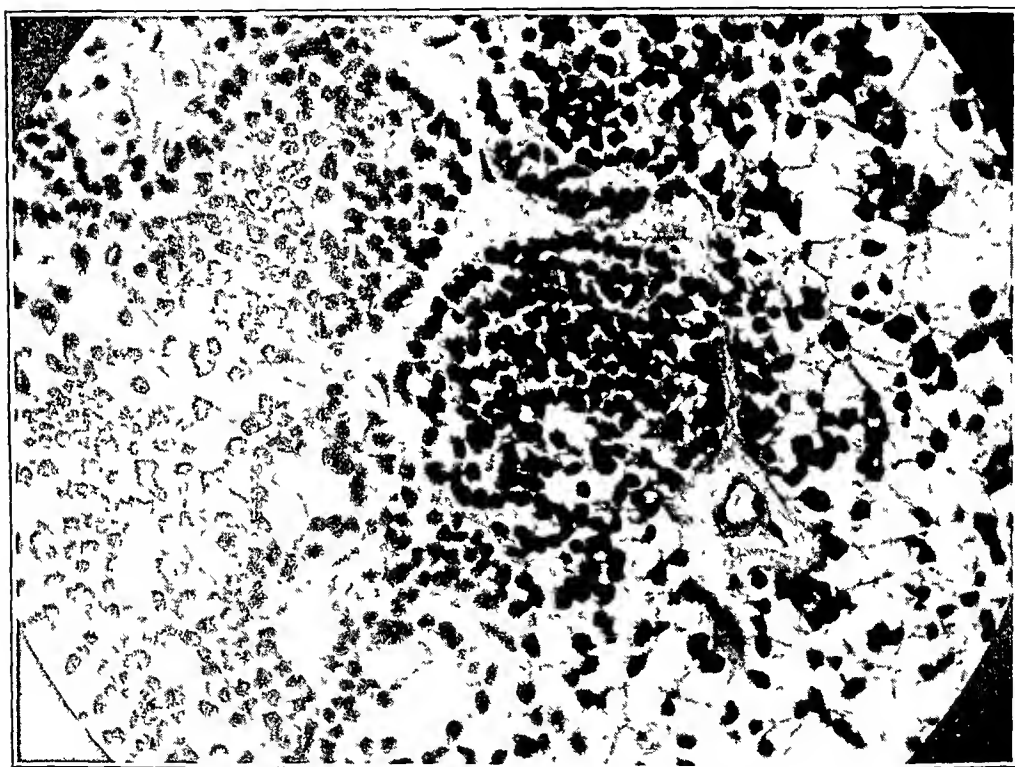


Fig. 5—Microscopic section of tumor.

During the oliguria the nonprotein nitrogen rose as high as 55 mg. per hundred cubic centimeters. Fortunately, 750 cc. of urine was secreted on the second day after the operation and 1,600 cc. on the third day; after this the diuresis increased to 2 liters daily and more.

The tenderness of the bones diminished day by day during the first three weeks after the operation, but the mental condition of the patient gave reason for anxiety. He became irritable and was often discontented with his surroundings, sometimes he took the hand of someone standing near and began to weep; there were hours in which he sat staring silently into space. An obvious tremor developed, which lasted sometimes for hours, followed by a short interval, when it began again. These symptoms developed after the operation. The patient suffered from insomnia, as well, but his sleep had been affected before the operation. His strange mental

the pseudo-osteomalacic final stage of Recklinghausen's disease. By this observation, moreover, the possibility of a tumor of the parathyroid was still further increased. Accurate palpation of the thyroid region showed that there was a small tumor, about the size of a plum stone, in the left lobe of the thyroid gland; this small growth moved up and down during the act of swallowing. A small adenoma of the thyroid itself could not be excluded, but on the basis of the facts mentioned it seemed clear that one could rather look on this small lump as a tumor of a parathyroid. At that time, in February, 1929, only the cases of Mandl and Gold were known. The remarkable results obtained by these surgeons led to the extirpation of the parathyroid tumor of this patient.

EXTIRPATION OF PARATHYROID TUMOR

On Feb. 28, 1929, Professor Lanz exposed the left side of the thyroid. In lifting the left lobe, a normal parathyroid was to be seen at the upper pole of the



Fig. 4.—Parathyroid tumor, cut open.

left lobe of the thyroid. At the lower pole a slight, somewhat yellowish protrusion could be seen on the spot where the lower parathyroid was to be expected, viz., where the thyroid artery enters the thyroid gland and the recurrent nerve comes into intimate contact with the thyroid capsule. From this situation a tumor, 25 by 14 mm. in size, was enucleated after incision of the capsule of the thyroid. As it is known that in Recklinghausen's disease the tumors of the parathyroid are nearly always solitary, the right lobe of the thyroid was not inspected.

On section, the tumor was found to consist chiefly of a yellowish compact parenchyma, while one-third was taken up by a cyst. Microscopic examination by Professor de Vries revealed that the growth was an adenoma of a parathyroid.

The further clinical course in this case showed that this adenoma of the parathyroid was the cause of the hypercalcemia.

Two symptoms which seemed favorable were noticed on the day after the operation, while two other symptoms gave reason for uneasiness. The first of the favorable symptoms was that the tenderness of the skeleton seemed to be less, the patient's legs could be moved a trifle more easily, and the thorax was also less painful when pressed. In the second place, the calcium content of the serum had gone down from 21.6 to 14.9 mg. per hundred cubic centimeters twenty-four hours after the operation; the decalcification of

an entire change had been brought about and clinical recovery has been obtained. The patient, it will be readily understood, remained a small, bent man with crooked legs, but the unfortunate invalid, chained to his bed in agony had been changed into a cheerful man, who had no more pain and who recorded with delight his daily improvement in walking.

COMMENT

In studying this peculiar case various details remain to be discussed. The subjective improvement was accompanied by an objective improvement in the calcium metabolism. Before the operation the calcium was dissolved from the bones through excessive secretion of parathyroid hormone by the tumor. This calcium circulated in the blood

TABLE 1.—*Determinations of Calcium in the Serum*

Before Operation		After Operation		
Date	Mg. per 100 Cc.	Date	Mg. per 100 Cc.	
2/13/29.....	23.6	3/ 1/29.....	14.9	Nonprotein nitrogen, 55 mg. per 100 cc.
2/14/29.....	22.8	3/ 5/29.....	8.50	Nonprotein nitrogen, 51 mg. per 100 cc.
2/22/29.....	19.0	3/17/29.....	7.20	
2/27/29.....	21.4	3/22/29.....	6.60	
2/27/29, nonprotein nitrogen	31	3/25/29.....	8.00	Calcium intravenously and parathy- roid extract subcutaneously
		4/ 4/29.....	7.67	Calcium intravenously and parathy- roid extract subcutaneously
		4/ 9/29.....	7.78	Calcium intravenously and parathy- roid extract subcutaneously
		4/20/29.....	9.86	Calcium intravenously and parathy- roid extract subcutaneously
		4/23/29.....	9.04	Calcium intravenously and parathy- roid extract subcutaneously
		5/ 1/29.....	8.83	
		5/15/29.....	8.15	
		5/28/29.....	8.04	
		6/ 4/29.....	9.66	
		7/12/29.....	10.56	Nonprotein nitrogen, 64 mg. per 100 cc.
		9/27/29.....	11.20	Nonprotein nitrogen, 51 mg. per 100 cc.

and caused the high calcium content of the serum and also of the urine, in which, as will be seen presently, abnormally large quantities of calcium were secreted. After the operation, the calcium content of the serum immediately went down. Table 1 shows how, as has already been mentioned, the calcium content of the serum fell within three weeks from 20 to 23 mg. to below 7 mg. per hundred cubic centimeters. Subsequently, by injecting calcium intravenously, and parathyroid extract subcutaneously, over a period of four weeks, the serum calcium was brought up to 9 mg. per hundred cubic centimeters. After this period, even without special treatment, the calcium content of the serum remained on a normal level. Following the operation the calcium secretion in the urine was completely changed (table 3). Before the operation, the patient was given a diet on which control experiments had showed normal persons secreted about from 30 to 100 mg. of calcium daily in the urine. This patient, however, when on this diet before his operation, secreted more than 400 mg. of calcium daily. After the

disturbance, which made nursing and feeding difficult, was explained by the rapid decrease of the calcium content of the serum. The amount of calcium per hundred cubic centimeters of serum was:

Before operation	21.4 mg.
24 hours after operation.....	14.9 mg.
5 days after operation.....	8.5 mg.
17 days after operation.....	7.2 mg.

These mental symptoms were apparently signs of impending tetany; when the calcium content of the serum had gone down to 7.2 mg. per hundred cubic centimeters, Chvostek's symptom, i. e., rapid contraction of the corner of the mouth and nostrils through percussing the facial nerve in front of the concha, could be observed for the first time. Five days later, that is, three weeks after the operation, the calcium content had gone down to 6.60 mg. per hundred cubic centimeters. The patient now lost all count of time and place; he screamed and yelled at night; he hardly recognized his surroundings, and if his osteomalacic limbs had permitted it, he would have tried to jump out of bed. Clearly, this amentia called for heroic measures. Although the patient had taken 4 Gm. of calcium lactate daily by mouth, since the operation, this apparently was not sufficient to keep the calcium content of the serum on a normal level. He now received injections of parathyroid extract-Collip subcutaneously and of a calcium compound intravenously.¹¹ The injection of 30 units of parathyroid extract daily and 10 cc. of the calcium compound twice daily raised the calcium content of the serum to 8 mg. per hundred cubic centimeters within three days. The patient became quieter, the amentia disappeared, and an agreeable euphoria gladdened both the patient and persons around him. This treatment proved necessary during a period of four weeks. The dosage was 30 units of parathyroid extract daily for the first two days, followed by 20 units for four days; for the remainder of the four weeks, the patient was given, on alternate days, 20 units and 10 units, respectively. The calcium was injected intravenously twice daily at the beginning of the treatment, and afterward only once a day. The calcium content of the serum went up to 9.04 mg. per hundred cubic centimeters after four weeks. The injections of parathyroid extract and calcium were stopped, and the calcium content of the serum remained on the normal level with daily doses of 4 Gm. of calcium lactate administered by mouth. The patient improved quickly during this period. The tenderness of the thorax was the first symptom to disappear, and the legs could now be moved more easily. The patient, further, was able to make active movements with his feet and toes. Six weeks after the operation, the patient was moved for the first time to a couch. At first, movement was accompanied by sighs and groans, but after some weeks, the patient for the first time tried walking between two nurses. Rapid improvement was made in this respect, so that at the beginning of August the patient was able to walk a short distance with no other assistance than two canes. Early in October he could walk for some minutes with one cane only. The tenderness of the skeleton had entirely disappeared. The patient's appetite was good; sleep and other vegetative functions were undisturbed. The edema of the legs had diminished considerably and had made room for hard induration, so that the patient was again able to wear his shoes. In short, as a result of the operation,

11. Helfenbergl describes this calcium compound as one which does not cause irritation even if a drop gets outside of the vein.

the improvement in the calcium metabolism, a calcification of the osteomalacic bones cannot also be observed. Mandl first reported that he had observed this in his case. Later, however, he had to admit that in spite of the really remarkable clinical improvement in his patient, roentgenologically only slight changes were noted on the skeleton. Gold

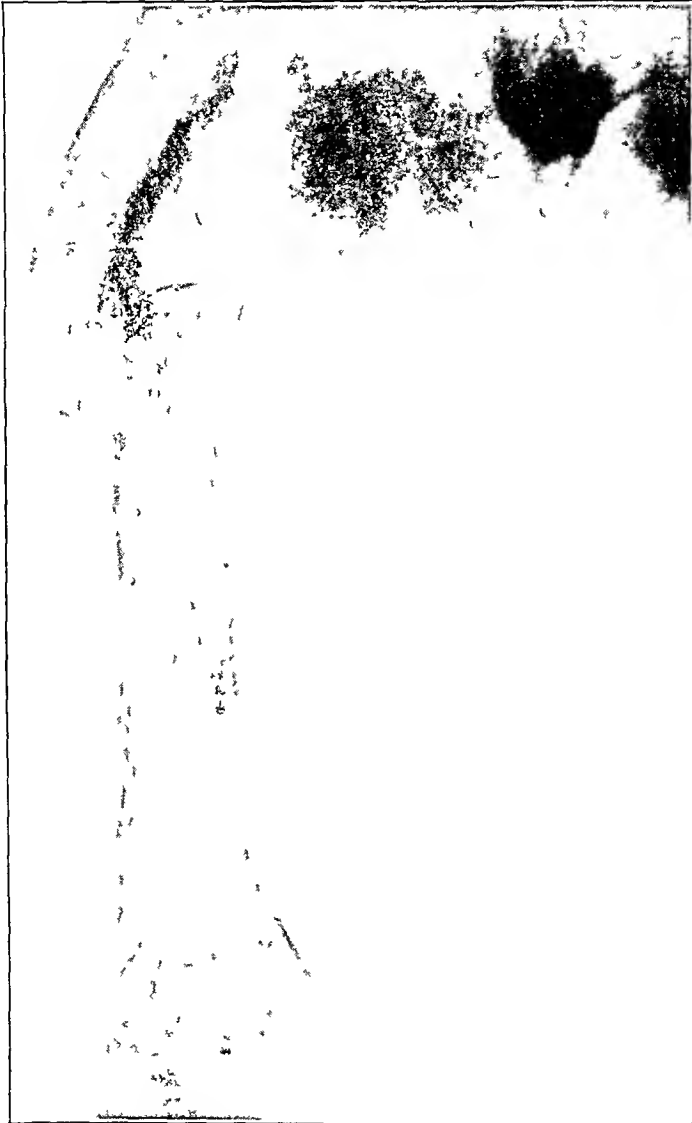


Fig 6—Femur, six months after operation

also came to this conclusion. The American authors, however, observed roentgenologic improvement in all their cases.

When examined a considerable time after the operation, the pelvis of the patient showed little change. In October, 1929, it was still a real osteomalacic, transparent, wedge-shaped pelvis. An important change could be observed, however, in the right femur. The fracture had healed with callus formation, and all the bone structures of the femur

operation only from 25 to 27 mg. of calcium was found in the urine every twenty-four hours, if the patient observed the aforementioned test diet (table 2). A fortnight after the operation the calcium secretion in the urine had become normal, which is clearly a proof that extirpation of adenoma of the parathyroid removed at the same time the cause of

TABLE 2.—*Other Observations on the Serum and the Blood Before Operation*

Substance	Mg. per 100 Ce.
Chloride	380
Calcium	21.4
Phosphorus pentoxide	2.1
Cholesterol	200
Lactic acid	30
Uric acid	5.8
Total albumin	6940
Albumin : globulin	7.02 : 2.98
Nonprotein nitrogen	31
Amino nitrogen	6.57
Alkali reserve51 per cent by volume
Fasting blood sugar.....	89
50 Gm. of dextrose by mouth:	
After ½ hour.....	125
After 1 hour.....	157
After 1½ hours.....	244
After 2 hours.....	150
Bleeding time.....	2½ minutes
Coagulation time:	
Beginning.....	7½ minutes
Total.....	8½ minutes

No glycosuria

TABLE 3.—*Results of Urinalysis with the Patient on a Calcium-Test Diet*

Date, 1929	Quantity, Ce.	Chlorine, Gm.	Calcium, Mg.	Phosphate, Mg.
Before operation				
2/24.....	2,400	2.88	411	883
2/25.....	2,300	3.2	393	925
2/26.....	2,500	4.04	425	874
2/27.....	2,400	2.06	432	971
2/28.....	2,200	3.2	322	880
After operation (2/28)				
3/14.....	2,300	5.1	2.2	402
3/15.....	1,900	4.1	25.0	346
3/16.....	2,000	4.2	37.0	375
4/22.....	1,380	3.76	23.5	420
4/23.....	1,500	3.45	28.8	564
4/24.....	1,560	4.1	39.1	538
5/10.....	1,100	36.7	
5/11.....	1,680	41.5	
5/23.....	1,700	37.6	
5/29.....	1,580	48.0	

the abnormal calcium metabolism, i. e., the cause of the dissolving of the calcium from the bones. It appears, further, that the pain was closely connected with this dissolving of the calcium from the skeleton. As soon as the calcium metabolism became normal, the pain in the bones disappeared. The other writers on the subject also observed, without exception, that their patients secreted abnormally great amounts of calcium in the urine before the operation, and that after the operation the calcium secretion went down to the normal rate of from 30 to 50 mg. per twenty-four hours. It may be asked whether, together with

hundred cubic centimeters. In October, 1929, the blood pressure was 135 systolic and 90 diastolic, and the nonprotein nitrogen 51 mg. per hundred cubic centimeters. There was, therefore, a decreased permeability of the kidneys; this is probably one of the reasons why the calcium content of the serum rose to an abnormal height.

It must be emphasized that the impaired kidney function alone cannot be the cause of the hypercalcemia. This cannot be the case because (1) after the operation, in spite of the impaired function of the kidneys, the calcium content of the serum went down immediately, and (2) in real uremia the figures for the serum calcium never reach this level. Therefore, the damaged kidney function can be only one of the causes of the abnormally high rate of hypercalcemia.

When one considers the fact that the calcium of the bone consists chiefly of calcium phosphate, it is obvious that a disturbance of the calcium metabolism must often involve disturbance of the phosphate metabolism. Collip has pointed out that if the calcium content of the serum increases under the influence of injections of parathyroid extract, the phosphate content of the serum decreases. In Wilder's case, the phosphate content of the blood was only 1.4 mg. per hundred cubic centimeters; in Barr's case, 1.4 mg.; in Dubois and Aub's case, 3.3 mg. and in the present case, only 2.1 mg., whereas the normal phosphate content is about 3 mg. While in Wilder's patient the phosphates of the blood remained low after the operation, viz., about 1.5 mg. per hundred cubic centimeters, in my patient it went up to 3.3 mg. five months after the operation.

Before the operation the phosphate secretion of the patient, on the same diet as that used in the examination for calcium, varied between 880 and 717 mg. daily. After the operation only from 364 to 560 mg. of phosphate was secreted daily in the urine. In Wilder's case the phosphate secretion also went down from 650 mg. daily before the operation to 300 mg. daily after the operation.

In discussing the present case, it has become evident that for the diagnosis of a parathyroid tumor with an osteitis fibrosa generalisata the finding of hypercalcemia is of the greatest importance. One has to point out, however, that in Wilder's case the calcium content of the serum hardly increased. Once a rate of 10.7 mg. of calcium per hundred cubic centimeters was found in the serum of the patient, and the highest figures found before the operation were between 11.8 and 13.7 mg. per hundred cubic centimeters.

On account of the fact that a parathyroid tumor existed in this case while the calcium content of the blood serum was nearly normal, in the future the calcium secretion in the urine, as well as the calcium content of the blood serum, will be analyzed in doubtful cases in order to avoid the exclusion of a parathyroid tumor, for the sole reason that the calcium content of the serum is about normal.

had become more compact. In February, 1930, the pelvis also showed extensive recalcification.

The extraordinary and striking arteriosclerosis of the patient remains to be mentioned. On the roentgenogram one can see the whole arteria femoralis appearing like a calcified snake in the muscle mass. On some roentgenograms even the ramification of the arteria femoralis profunda is to be seen. This gives one the impression that the vascular wall had greedily absorbed the excessive quantity of calcium in the serum. Clinical improvement did not change this marked arteriosclerosis; the calcium was apparently firmly embedded in the vascular wall.

The question as to why the calcium content of the serum of this patient was so much higher than the amounts which the other authors found in their cases of parathyroid tumor with osteitis fibrosa generalisata calls for special discussion. While in this patient the calcium content in the serum fluctuated between 19 and 23 mg. per hundred cubic centimeters, Gold found 13 mg. per hundred cubic centimeters, Du Bois and Aub 14.5 and 16 mg., Barr 16 mg. and Wilder 11.2 mg. In order to explain the much greater hypercalcemia in my patient, one has to bear in mind in the first place that he had a much more advanced case of osteomalacia than did the other patients, in whom more symptoms of real osteitis fibrosa generalisata were found. For this reason, probably, the decalcification was more pronounced in this patient, and thereby, more calcium was dissolved from the bones. In the second place, one must also call to mind that the patient had damaged kidneys. Many patients suffering from osteitis fibrosa generalisata produce calcium stones in the kidneys (e. g., Barr's patient) through large amounts of calcium secreted with the urine. Neither roentgenologic nor clinical symptoms of kidney stones were to be found in this patient. His pyuria, however, was a sign of pyelonephritis, which may or may not have been calculous, but through which the excretory function of the kidneys suffered. This was proved by the nonprotein nitrogen of the blood. The nonprotein nitrogen of the blood of 31 mg. per hundred cubic centimeters before the operation was too high, when one considers that this patient was then closely confined to his bed and was on a much restricted diet. During the anxious days of the oliguria directly after the operation, the nonprotein nitrogen of the blood rose to 55 mg. per hundred cubic centimeters. When the diuresis started again, the nonprotein nitrogen of the blood did not go down, but remained on this level. To make quite certain, the nonprotein nitrogen of the blood was reexamined in August, 1929. At that time the patient was exceedingly well; he had a normal blood pressure and a tremendous appetite and did not complain of headache or nausea. Notwithstanding this general improvement in health, the urea content of the blood was then 1 Gm. per liter, and the nonprotein nitrogen of the blood 64 mg. per

developed two days after the operation, and many months afterward she still needed calcium and parathyroid extract. The development of tetany after the operation can be explained in various ways. The possibility of an injury to the other parathyroids during the operation is obvious. In the present case, however, the right side of the thyroid was not exposed. The parathyroids situated at the right side could not be injured, therefore, during the operation. The possibility also exists that this patient had no parathyroids on the right side, and that immediately after the operation the only remaining left parathyroid gland was not able to regulate the calcium metabolism adequately. Meanwhile, if one does not wish to use the unproved hypothesis that the patient had no parathyroids on the right side, another possibility may be considered. After the operation the decalcified skeleton may absorb calcium from the blood with so much avidity that through this rapid absorption the calcium content of the serum descends below the critical level, and symptoms of tetany appear; even three normal parathyroids would then be unable to regulate this absorption through the skeleton. Only a mechanism of this order could explain the symptoms of tetany if the patient had normal parathyroids on the right side. In Barr's case there was a strong argument in favor of this conception; up to 100 units of parathyroid extract were injected daily into his patient when symptoms of tetany developed after the operation. In spite of these injections, her condition and the symptoms of tetany grew worse. At that time this patient had sufficient parathyroid hormone (injected), but nevertheless suffered from tetany. Only when calcium chloride was injected intravenously at the same time as the parathyroid extract did improvement occur. Before the treatment by injections of calcium Barr's patient was given 4 Gm. of calcium by mouth; this oral administration had no influence on the tetany. This observation is also in favor of the hypothesis that even with sufficient parathyroid function, in other words, with sufficient parathyroid extract, tetany may arise in these patients through excessive absorption of calcium from the serum.

Parathyroid extract was given to my patient only when his condition became precarious. Perhaps tetany could have been avoided altogether if parathyroid extract had been given earlier. It is clear, however, that increase of the calcium content of the serum under the influence of parathyroid extract is brought about by resorption of calcium from the bones, an occurrence that I wished to avoid. In future cases I shall without doubt inject calcium intravenously directly after the operation. It seems evident that after the long negative calcium balance, there exists such a calcium hunger of the organism that in these conditions administration of calcium by mouth is not sufficient.

Because there is danger of tetany after an operation for a parathyroid tumor, it may be asked whether recovery can occur without

Furthermore, stress must be laid on the fact that although the calcium content of the serum and that of the urine form important elements, clinical experience still remains the chief factor in the ultimate diagnosis. As a matter of fact, in other diseases a high calcium content of the blood may be present, for example, in malignant myelomas (Barr). At the Mayo clinic this has been observed in polyglobulia, and it has also once been described in a case of rachitis tarda.

On the other hand, highly increased calcium secretion in the urine, with a normal calcium content of the blood serum, is almost constantly found by Aub in cases of exophthalmic goiter; a similar condition to that found in Wilder's case then arises. In short, diagnostic errors may easily occur, and however important the data of the chemical analysis of blood and urine may appear, in the diagnosis of a parathyroid tumor clinical skill and experience must play an even more important part.

Sometimes the tumor of the parathyroid may be discovered through palpation before operation; sometimes, however, a parathyroid tumor may be present which is not revealed through palpation (Mandl, Gold). Wilder's patient had a malignant adenoma of the parathyroid (Wellbrock¹²). In Du Bois' case no tumor was found even at operation. Clinical recovery was obtained by the removal of two normal-looking parathyroids.

The oliguria which was observed in the present case after extirpation of the tumor deserves special mention. Gold also mentioned oliguria several days after the operation. In this connection McCann's experiments must be recalled;¹³ by injections of parathyroid extract he was able to obtain the same diuretic effect, which may be observed also after the administration of thyroid extract to patients with edematous kidneys. The hormone of the parathyroid apparently has an influence on the physicochemical properties of the tissues. In this way it may be understood how after removal of the principal source of the parathyroid extract, i. e., the adenoma, in the case reported, the output of urine diminished. The patient evidently was accustomed to excessive quantities of parathyroid hormone. It took several days before the organism became used to the much smaller quantity of parathyroid hormone secreted by the remaining parathyroids.

Finally, there is the most important problem, the fact that severe tetany can arise after removal of a parathyroid tumor. Beck has described how through tetany he lost a patient after he had removed a tumor of a parathyroid gland.¹⁴ In Barr's patient also serious tetany

12. Wellbrock: *Endocrinology* **13**:285, 1929.

13. McCann, W. S.: Diuretic Action of Parathyroid Extract-Collip in Certain Edematous Patients, *J. A. M. A.* **90**:249 (Jan.) 1928. Hueper, W. C.: The Diuretic Action of the Parathyroid Extract, *Arch. Int. Med.* **44**:374 (Sept.) 1929.

14. Beck: *Arch. f. klin. Chir.* **152**:123, 1928.

EXPERIMENTAL GASTRIC ULCER

THE EFFECT OF THE CONSISTENCY OF THE DIET ON HEALING *

GORDON B. FAULEY, M.D.

AND

A. C. IVY, M.D.

CHICAGO

Clinical experience and experimental observations indicate that the consistency of the diet may have a bearing on the healing of gastric ulcers.

That the physician believes the consistency of the diet is an important therapeutic item in the management of patients with ulcers is shown by the fact that a liquid or soft diet, with or without a preceding period of starvation, is used in all the generally accepted therapeutic procedures. Bolton,¹ in his book on "Ulcer of the Stomach," stated that in his opinion "there is no doubt that diet influences the production and propagation of ulcer of the stomach." He stated that "excessive amounts of imperfectly masticated, and hurriedly swallowed food of 'indigestible' quality, although alone being unable to produce the initial lesion, yet are able to assist in so doing, and in promoting the extension and delaying the healing of an ulcer of the stomach."

The fact that increased motility of the stomach associated with gastric retention delays the healing of experimentally produced acute ulcers of the stomach has been demonstrated by Bolton,² Friedman and Hamburger,³ and Ivy,⁴ who produced acute lesions of the stomach in dogs with partial pyloric stenosis, although all are agreed that partial stenosis per se does not give rise to the initial lesion.⁵ The relative hyperacidity and hypernormal secretion associated with partial pyloric

* Submitted for publication, March 22, 1930.

* From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. Bolton: *Ulcer of the Stomach*, New York, Longmans, Green & Company, 1913.

2. Bolton: *Proc. Roy. Soc. Lond.* **82**:236, 1909.

3. Friedman, J. C., and Hamburger, W. W.: *Experimental Chronic Gastric Ulcer*, J. A. M. A. **63**:380 (Aug. 1) 1914.

4. Ivy, A. C.: *Contributions to the Physiology of the Stomach*, Arch. Int. Med. **25**:6 (Jan.) 1920.

5. Ivy, A. C.; Droegemueller, E. H., and Meyer, J. L.: *Effect of Experimental Pyloric Stenosis on Gastric Secretion*, Arch. Int. Med. **40**:434 (Oct.) 1927.

operation. Regnier¹⁵ made an important observation. He obtained considerable improvement in a patient with Recklinghausen's disease by giving large doses of irradiated ergosterol. Gold remarked in the discussion that he doubted the diagnosis of osteitis fibrosa generalisata in Regnier's case, but Kienböck declared subsequently that there was no doubt that Regnier's diagnosis was correct. Blumgart¹⁶ of Boston noticed improvement in a case of osteomalacia after treatment with irradiated ergosterol, but he stated that his patient suffered from rachitis tarda. On the other hand, other clinicians were not successful with this treatment. Wilder's patient lived from the end of May, 1927, to May 16, 1928, on a diet which contained a great deal of vitamin D; on this diet, combined with treatment by alpine light, the patient grew stronger and heavier, and the calcium and phosphate balance became positive. The calcium content of the serum, however, did not change, and the pain remained the same, so that an operation finally had to be performed. The patient described here also took irradiated ergosterol for some time before his operation, but without success. It is clear that even if a trial of irradiated ergosterol is justified, operation for the tumor of the parathyroid may still be necessary in many cases.

In conclusion, it may be stated with confidence that the lives of patients suffering from osteitis fibrosa generalisata can be saved by removal of the adenoma of the parathyroid. This operation will protect them from severe illness of many years' duration, an illness which leads, as a rule, to a cachectic end-stage and ultimate death in violent pain. Finally, it must be stressed that special care be taken after operation to prevent lethal tetany.

SUMMARY

The following points were noted in a patient suffering from extensive decalcification of the bones, combined with violent pain:

1. The illness began as osteitis fibrosa generalisata. Therefore there existed a pseudo-osteomalacic end-stage of Recklinghausen's disease.
2. There was a great increase in the calcium content of the serum. The deviation was considered to be a symptom of hyperfunction of the parathyroids.
3. There was a small swelling in the thyroid.

On account of these facts, a tumor of a parathyroid gland was suspected, and was found during operation. After extirpation of this small tumor, clinical recovery occurred.

15. Regnier: *Fortschr. a. d. Geb. d. Röntgenstrahlen* **39**:696, 1929.

16. Blumgart: Personal communication to the author.

In nine rabbits we produced ulcers 1.5 to 2 cm. in diameter on the dorsal or posterior wall of the stomach. In this operation it was necessary to push the contents of the pyloric antrum back into the fundus, where it was held by a low tension clamp during the period of the operation. The opening in the ventral or anterior wall made it possible to excise the piece of mucosa from the dorsal wall of the stomach; then the opening in the anterior wall was closed. The mortality from this procedure was fairly high, about 30 per cent due to intragastric hemorrhage, pneumonia or gastric paresis.

The rabbits were fed either a rough diet or a soft diet. The rough diet consisted of the usual stock ingredients; alfalfa hay, oats and raw carrots. The soft diet consisted of bread, milk and boiled carrots finely mashed. The rabbits to be placed on the soft diet were kept on that diet from one to two weeks prior to operation. We found that the stomach of these rabbits at the time of operation usually contained definitely less material than those fed on the hard diet, and the contents were more fluid in consistency. Some rabbits did not do well on this diet and died prematurely, that is, before the thirty day postoperative period had elapsed. The rabbits were killed after thirty days, and the stomach was examined for the presence or absence of an ulcer, its diameter being measured.

RESULTS

Simple Lesion on Posterior Wall.—In the nine rabbits in which a lesion was produced by excision of the mucosa of the posterior wall, all ulcers were healed in thirty days, five rabbits being fed on the soft diet and four on the rough diet.

In two of the four on the rough diet, an anterior as well as a posterior lesion was also produced. In these two rabbits the lesion on the posterior wall had completely healed, but in both cases the lesion on the anterior wall, which had been closed with silk, had developed into a chronic ulcer which had perforated into the liver.

These results show that the acute lesion of the posterior wall which contained no silk suture healed in spite of the consistency of the diet, and indicate that the silk suture plus the rough diet was the probable cause of the delayed healing.

In order to test this possibility further, in thirty-nine rabbits we made anterior lesions, closing them with a silk suture, nineteen being on a soft diet and fourteen on a rough diet.

On a Soft Diet With Anterior Lesion Plus Silk Suture.—Of the twenty-two rabbits used, seventeen lived through the thirty day test period, five dying prematurely at two, nineteen, eighteen, twenty-three and twenty-six days, all with ulcers that had not healed. Of the seventeen that were killed on the thirtieth day, only three had ulcers. The scars were easily found, and in some the scar showed a papillomatous-like overgrowth of the mucosa, as observed by Shapiro and Ivy⁹ in their study of ulcer in the rabbit.

9. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer, Arch. Int. Med. **38**:237 (Aug.) 1926.

stenosis may have been a contributing factor in delaying healing, but not a fundamental one when viewed in the light of Dragstedt's ⁶ finding that an acute ulcer produced in a gastric pouch so made as to retain its gastric secretion healed as quickly as an acute ulcer produced in a pouch in which the gastric juice was not retained. It was further shown by Ivy ⁷ that simple manipulation with the finger of an acute lesion of the mucosa of a pouch of the pyloric antrum, in the absence of acid, delayed the healing of the acute lesion. The same manipulation with a cotton pledget soaked in 0.4 per cent solution of hydrochloric acid has the same effect as manipulation, except that bleeding occurs earlier. This demonstrates that a mechanical factor can delay the healing of an acute lesion of the gastric mucosa, and that acid makes the ulcer more irritable or susceptible to bleeding.

It is an established fact that coarse particles of food remain in the stomach longer than fine particles, which obviously results in more prolonged motor activity of the stomach and increases the trauma to an acute lesion of the mucosa. This would be pronounced in a patient with pylorospasm.

Although the evidence indicates that the consistency of the diet has an important bearing on the healing of gastric ulcer, we have been unable to find any experimental work bearing directly on this problem.

Our attention was attracted by the work of Ferguson,⁸ who was able by a certain procedure to produce in rabbits a lesion of the gastric mucosa which persisted for from two to eight months or longer, and which manifested the gross and histologic characteristics of a chronic ulcer. Since it is well known that the rabbit's stomach is filled constantly with oat hulls and very rough material, it occurred to us that we had at hand a method for studying the effect of the consistency of the diet on the healing of gastric ulcers.

METHODS FOR EXPERIMENTAL WORK

Ferguson's method is to expose the ventral wall of the stomach. An incision 3 or 4 cc. in length is made through the serosa and muscularis down to the mucosa in the region of the pyloric antrum. The mucosa is separated from the muscularis by undercutting, so that an area of mucosa 2 cm. in diameter is freed and exposed. This area of mucosa is then excised and the muscularis and serosa closed with a silk suture. This results in an ulcer which quite uniformly measures from 1.0 to 1.5 cm. in diameter, a statement we are able to make because a number of our rabbits died of pneumonia within a day or two after the operation.

6. Dragstedt, L. R.: Contributions to the Physiology of the Stomach, *J. A. M. A.* **68**:330 (Feb. 3) 1917.

7. Ivy, A. C.: Studies on Gastric and Duodenal Ulcer, *J. A. M. A.* **75**:1540 (Dec. 4) 1920.

8. Ferguson, A. N.: Cytological Study of Regeneration of Gastric Glands Following Experimental Removal of Large Areas of Mucosa, *Am. J. Anat.* **42**: 403, 1928.

to establish permanent relations with the underlying capillaries which is their source of nourishment; in other words, we believe that factors which tend to disturb the blood supply or nutrition of the proliferating mucosal cells are responsible for delaying healing.

Rôle of Gut Suture Versus Silk Suture.—It is well known that a silk suture is not absorbed but is encapsulated by connective tissue; whereas a gut suture, although it causes some foreign body reaction, is finally absorbed or causes less connective tissue proliferation. Because of this difference an ulcer was produced in the anterior wall, the



Fig. 1 (rabbit 51)—A three day lesion showing the type of lesion produced; this one measured 8 by 10 mm.

incision was closed with gut instead of silk, and the rabbits were placed on a rough diet. This was done in four rabbits, with the result that in three of the four, typical ulcers were present. In the other, almost complete healing (no pitting, ulcer defect 1 by 2 mm) had occurred. These results show that the gut suture caused sufficient connective tissue proliferation or a sufficient amount of some unknown disturbance to delay healing. They do not prove, however, that no difference exists between gut and silk in delaying healing; to settle this point, more rabbits must be used and a longer postoperative period allowed as a test period.

These results show that the silk suture per se is not the cause of the delayed healing noted in the foregoing and following experiments, because healing occurred on this diet with the silk encapsuled in situ in the scar.

On Rough Diet with Anterior Lesion Plus Silk Suture.—There were twelve rabbits with anterior lesions on the rough diet. When killed on the thirtieth day, all had typical chronic ulcers varying from 3 to 8 mm. in diameter. One rabbit that was killed at forty-two days showed complete healing. Others kept for longer periods than thirty days failed to show complete healing. Ferguson¹⁰ recently showed us an ulcer made according to his method, the one we used, which had not healed in two years.

These results on the soft and rough diet with the anterior lesion show conclusively, we believe, that the consistency of the diet is an important factor in determining the healing time of the ulcer, provided that an additional factor (the silk suture or connective tissue factor) tending to delay healing is present. That the rough diet is not the sole factor is shown by the fact that the simple acute ulcer on the posterior wall (without the silk) healed in thirty days, irrespective of the consistency of the diet. These results also demonstrate that the reason why Ferguson was able to obtain chronic ulcers consistently by his method was that he used a rough diet in addition to the silk suture, which is not absorbed but encapsuled by connective tissue.

The fact that the amount of healing on the rough diet varies from one rabbit to another, is best explained on the basis of a difference in the growth capacity of the fibroblasts and mucosal cells in the different rabbits, rather than on the basis of the variation in the size of the acute lesion. A faster rate of growth and maturity of the connective tissue elements would reduce the blood supply to the more slowly growing and more highly differentiated mucosal cells and hence make it more difficult for the mucosal cells to cover the defect. The silk, being non-absorbable and acting as a foreign body, excites fibroblastic reaction. In the absence of this excessive connective tissue growth, the ulcer heals irrespective of the diet. The observations of Dragstedt and Vaughn¹¹ on the production of chronic gastric ulcer in the dog by taking a number of stitches with silk in the base of an acute ulcer further supports this explanation, especially since in some dogs, in spite of the suture, the ulcer healed, while in others it became chronic. The rough diet, with the associated augmented motility, renders it difficult for the mucosal cells to obtain a foothold on the base of the ulcer and

10. Ferguson, A. N.: Personal communication to the author.

11. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies, Arch. Surg. 8:791 (May) 1924.

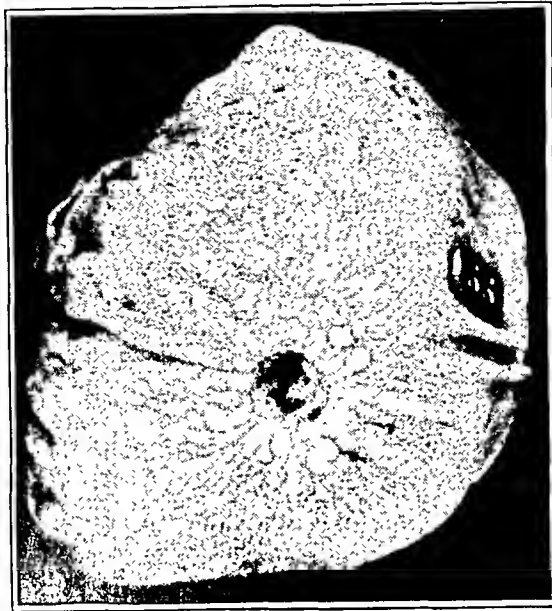


Fig. 4 (rabbit 66).—Ulcer 10 by 10 mm., silk suture on the anterior wall of a rabbit on diet of dry rolled oats.



Fig. 5 (rabbit 19).—Ulcer 8 by 8 mm., gut suture on the anterior wall of a rabbit on a rough diet.

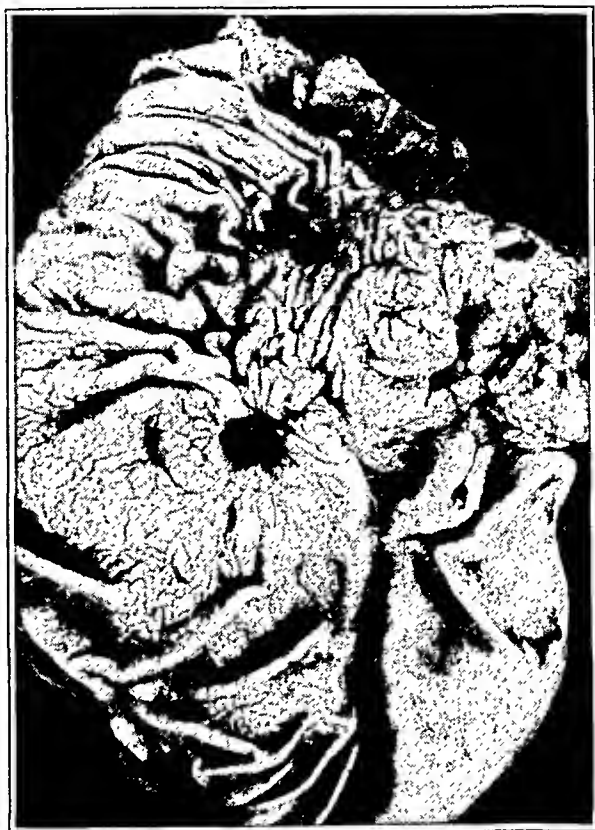


Fig. 2.—Ulcer 7 by 7 mm., silk suture on the anterior wall, which perforated into the liver in rabbit on rough diet.



Fig. 3 (rabbit 22).—Ulcer 6 by 6 mm., silk suture on the anterior wall of rabbit on rough diet.

observed a chronic ulcer to occur. The foregoing statement for animals is true to some extent, at least, for man. However, given a man with a chronic ulcer, or a man with a lesion of the stomach plus the factor or factors responsible for the chronicity, our results from experiments on the rabbit indicate that a soft diet would facilitate the healing of the gastric lesion.

SUMMARY

A simple ulcer of the rabbit's stomach (1.5 to 2 cm. in diameter) produced by excision heals within thirty days, irrespective of the consistency of the diet.

Healing of Acute Lesion of Gastric Mucosa As Influenced by a Rough and Soft Diet

Rough Diet			Soft Diet		
Rabbit Number	Days Post-operative	Ulcer Size in Mm.	Rabbit Number	Days Post-operative	Ulcer Size in Mm.
17	30	1.5 × 3	38	31	Complete healing
22	30	6 × 6	5	30	2 × 6
10	30	6 × 7	25	30	Complete healing
18	30	2 × 3	42	30	Complete healing
51	30	1.5 × 3	47	30	Complete healing
67	30	2 × 3	77	31	2 × 4
8	30	8 × 10	76	30	Complete healing
1	30	5 × 9	24	30	Complete healing
4	30	3 × 4	26	30	Complete healing
88	30	1 × 2	74	30	Complete healing
25	30	3 × 4	85	30	Complete healing
73	30	5 × 6	71	30	Complete healing
100	42	Complete healing	34	30	1.5 × 3
			55	30	Complete healing
			97	30	Complete healing
			78	32	Complete healing
			44	30	Complete healing
			89	19	3 × 4
			80	18	7 × 10
			7	2	15 × 20
			6	23	2 × 5
			61	26	2 × 3

A similar ulcer, but with a silk suture in its base, will heal if the rabbit is fed a soft diet, but will tend to become chronic if the rabbit is fed a rough diet. We have confirmed Ferguson's⁸ observation that if an acute lesion is made by his method and the rabbits are kept on a rough diet, a chronic ulcer results in numerous instances.

The consistency of the diet has an influence on the healing of an ulcer of the stomach, if other factors that tend to delay the healing are operating simultaneously.

These results indicate that in chronic ulcer in man, a soft diet would facilitate the healing of the ulcer, which confirms clinical experience and supports the use of a diet of the character of that employed in the generally accepted therapeutic procedures for gastric ulcer.

Specific Qualities of the Diet.—Other factors than the consistency of the diet must be considered, such as the fat content which inhibits the formation of gastric secretion during the early part of the digestive period and the buffer value of the food, or the capacity the food possesses of combining with free acid, and roughage.

We have not as yet performed experiments to analyze the importance of all these factors, but we have performed an experiment relative to the roughage factor.

Four rabbits were placed on a diet consisting solely of Quick Rolled Oats in the dry form, which avoided the roughage from the oat hulls, hay and lumps of raw carrots. An ulcer was produced in the anterior gastric wall as described, the defect in the muscularis being closed with silk. When the stomach of these rabbits was opened, the contents were found to be as pasty and as dry as that found in the rabbits fed

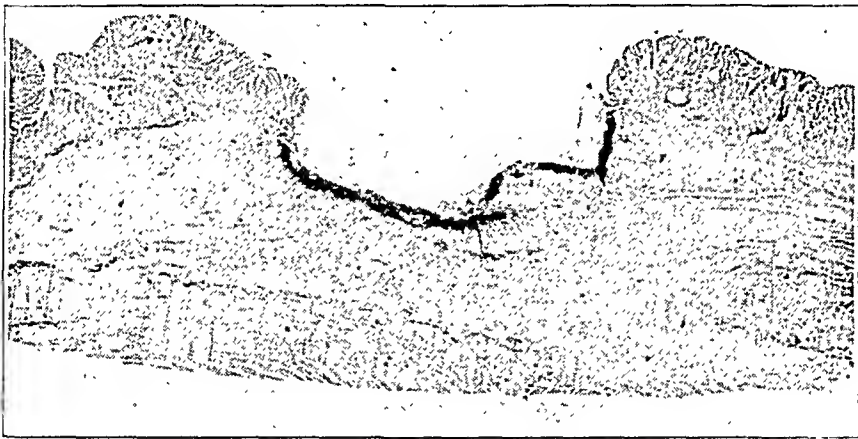


Fig. 6 (rabbit 66).—Photomicrograph of ulcer in figure 4. The steep edge of the ulcer was the edge nearest the cardia; $\times 6$.

on the oats and hay diet. An ulcer was found in all four rabbits when they were killed at the thirty day period. This shows that a high percentage of roughage alone is not the only factor operating in the rough diet, and that the fluidity of the gastric contents is a factor which must be considered as important.

Other experiments are under way to test further the fluidity, fat and food buffer factors.

COMMENT

Every investigator is agreed that simple or uncomplicated acute lesions of the gastric mucosa of animals heal rapidly and almost without failure. Those of us who have done considerable gastric analysis on normal man, withdrawing the contents by suction, have not infrequently observed streaks of blood and pieces of mucosa in the withdrawn fluid, and without changing the diet in any way have not

These authors, however, do not suggest this as evidence in regard to the duration of the life of reticulocytes in the blood stream. Seyfarth and Jürgens⁴ noted that the cells with "substantia granulofilamentosa" gradually diminished in the blood stream of mouse embryos with increasing age of the embryos and continued to diminish after birth. Cohn, and Minot and their collaborators⁵ suggested from their observations on the reticulocyte response in pernicious anemia following liver therapy, that reticulocytes in the blood may not lose the reticular material for from five to ten days.

Observations concerning the direct effect of liver extracts, which are capable of producing complete remission in pernicious anemia, on the maturation of reticulocytes in vitro have been essentially negative.⁶ These observations led to a study of the changes in the number and appearance of the reticulocytes under certain experimental conditions. The results of this study had a direct bearing on the life of reticulocytes after they enter the blood stream and are presented here.

METHODS

Blood containing large numbers of reticulocytes was obtained from two sources: (1) human patients, especially those with cases of pernicious anemia at the peak of the reticulocyte rise following liver therapy, and (2) rabbits that either had been bled from the ear every other day or had been given phenylhydrazine intraperitoneally. The blood was collected under sterile precautions, placed in a small sterile flask containing glass beads and defibrinated by gentle shaking. Usually 0.5 cc. of defibrinated blood was placed in a small sterile test tube, corked and placed in an incubator at 37 C. As a rule, five such preparations were used for each blood to be tested.

Smears of blood were made on glass cover-slips and stained supravitaly with brilliant cresyl blue and counterstained with Wright's stain after the methods described by Hawes⁷ and Cunningham.⁸ Thus permanent preparations of stained reticulocytes were available for prolonged observation and future reference. Usually, 1,000 erythrocytes were counted, areas on both cover slips being used, and the reticulocyte percentage was determined.

4. Seyfarth, C., and Jürgens, R.: Untersuchungen über das Verhalten der vitalgranulierten roten Blutzellen (Retikulocyten) bei Embryonen und Neugeborenen, *Virchows Arch. f. path. Anat.* **266**:676 (Jan.) 1928.

5. Cohn, E. J.; Minot, G. R.; Alles, G. A., and Salter, W. T.: The Nature of the Material in Liver Effective in Pernicious Anemia: II, *J. Biol. Chem.* **77**:325 (May) 1928.

6. Heath, C. W., and Daland, G. A.: The Basophilic Substance of Young Red Blood Cells: The Influence of Solutions of Different Substances upon the Supravital Staining with Brilliant Cresyl Blue, to be published.

7. Hawes, J. B.: A Study of Reticulated Red Blood Corpuscles by Means of Vital Staining Methods, Its Relation to Polychromatophilia and Stippling, *Boston M. & S. J.* **161**:493 (Sept.) 1909.

8. Cunningham, T. D.: A Method for the Permanent Staining of Reticulated Red Cells, *Arch. Int. Med.* **26**:405 (Oct.) 1920.

THE LIFE OF RETICULOCYTES

EXPERIMENTS ON THEIR MATURATION *

CLARK W. HEATH, M.D.

AND

GENEVA A. DALAND, B.S.

BOSTON

The life history of red blood corpuscles has fascinated many investigators. A large amount of literature has accumulated regarding the development of red blood corpuscles, one phase of which concerns cells containing basophilic substance or, when supravitaly stained, reticular substance and commonly known as reticulocytes. Since Theobald Smith¹ first suggested that these were young cells rather than degenerative forms of the adult red blood cell, an abundant amount of evidence has been presented which indicates clearly that the basophilic substance is a sign of youthfulness.

Some of the evidence that reticulocytes are less mature than non-basophilic erythrocytes is well founded on multiple observations in states of anemia in which an increase of reticulocytes in the peripheral circulation precedes an increase in nonreticulated erythrocytes. Nevertheless, little information is available concerning the fate of such young cells: the duration of their stay in the circulation, the disposal of the basophilic substance and whether they develop into nonbasophilic erythrocytes or are destroyed. Without doubt, under normal conditions in adult persons any maturation of the majority of these cells must take place in the bone-marrow. Indirect evidence favors the opinion that reticulated cells which reach the circulation remain for a few days and mature there. Pepper² observed that reticulocytes in rabbits' blood kept in the incubator gradually diminished in number and disappeared by the third day. Morawitz and Denecke³ stated that if blood is allowed to age in vitro, these cells disappear after from one to two days.

* Submitted for publication, Feb. 1, 1930.

* From the Thorndike Memorial Laboratory of the Boston City Hospital and the Department of Medicine of the Harvard Medical School.

1. Smith, Theobald: On Changes in the Red Blood-Corpuscles in the Pernicious Anemia of Texas Cattle Fever, *Tr. A. Am. Phys.* **6**:263, 1891.

2. Pepper, O. H. P.: Observations on Vitaly Stainable Reticulation and Chromatic Granules in Erythrocytes Preserved in Vitro, *Arch. Int. Med.* **30**:801 (Dec.) 1922.

3. Morawitz, P., and Denecke, G.: *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1926, vol. 4, p. 53.

and those of pernicious anemia. Therefore, it may be assumed that, at least in this regard reticulocytes are of the same general nature no matter what the cause inciting their increased output into the circulation.

If the results of any of these experiments are plotted with the percentages of reticulocytes as ordinates and the period of time as abscissas, as in figure 1 (experiment 16, table 1), there results a typical exponential curve. If this curve is plotted with the logarithms of the reticulocyte percentages as ordinates, the result is a straight line. This type of curve is typical of many simple biologic and chemical phenomena, and is characteristic of senescent phenomena.

TABLE 1.—*The Decrease of Reticulocytes in Vitro at 37 C.*

Diagnosis	Ex- peri- ment	Patient	Time Relative to Peak of Reticulocyte Response	Percentage of Reticulocytes*					
				Start Before Incuba- tion	24 Hrs. After Incuba- tion	48 Hrs. After Incuba- tion	72 Hrs. After Incuba- tion	96 Hrs. After Incuba- tion	120 Hrs. After Incuba- tion
Pernicious anemia	1	Ty	1 day before	33.3	17.5	7.3	3.8
	2	Ty	1 day after	29.5	9.3	6.3	3.2
	3	Ld	1 day before	22.1	8.6	6.3	3.5
	4	Br	2 days before	23.3	18.1	15.1	12.3	5.7	...
	5	Br	Day of peak	42.1	27.6	20.5	14.0	...	5.6
	6	Br	2 days after	34.5	21.0	13.0	6.7	2.2	...
	7	Cn	2 days after	15.2	3.3	2.0	0.8
	8	Gn	1 day before	26.7	14.4	9.7	...	3.1	...
	9	Gn	Day of peak	36.8	11.5	...	3.7	...	1.1
	10	Ky	1 day before	23.2	17.6	8.5	4.6	1.9	...
Purpura hem- orrhagica	11	Wx	26.2	15.3	11.3	4.8	0.8	...
	12	17.3	7.8	4.4	3.1	0.7	...
Chronic familial hemolytic jaundice	13	Ce	10.8	3.5	1.5	0.7
	14	Yk	39.2	17.7	11.4	8.0
Normal	15	Hh	0.6	0.5	0.0
Rabbits rendered anemic by bleeding	16	R ₁	32.5	9.6	5.4
	17	R ₂	20.1	9.0	4.4	2.0	0.4	...
	18	R ₃	18.6	5.6	4.8	1.6	0.2	...
Rabbits into which injections of phenylhydra- zine were made	19	R ₄	21.9	9.6	9.4	5.1
	20	R ₅	24.3	9.8	8.4
	21	R ₆	19.5	11.5	7.6
	22	R ₇	30.3	18.6	14.8	4.8

* The results reported are the averages for the percentages of reticulocytes from five tubes in all experiments with the following exceptions: 18 and 21, four tubes; 14, three tubes; 10 and 8, two tubes; 15 and 22, one tube each.

DECREASE OF RETICULOCYTES IN THE PLEURAL CAVITY OF THE RABBIT

In order to place the cells under more normal physiologic conditions, from 8 to 10 cc. of defibrinated blood rich in reticulocytes was injected into the pleural cavity of rabbits by the following technic: The skin over the back in the lower thoracic region was shaved, procaine hydrochloride was injected and the pleura was exposed between the seventh and eighth ribs under sterile precautions. At varying periods over the course of two or three days, a small needle was inserted into the eighth or ninth interspace, and a drop or two of the previously injected blood was with-

DECREASE OF RETICULOCYTES IN VITRO AT 37 C.

A study of table 1 shows that at 37 C. the number of cells with reticular substance diminishes gradually over the course of three or four days. During the first few days the cells remained in good condition. At the end of four days, especially in the case of rabbits' blood, there was a tendency to hemolysis, sometimes marked, and the red cells tended to become distorted, so that further observations were not reli-

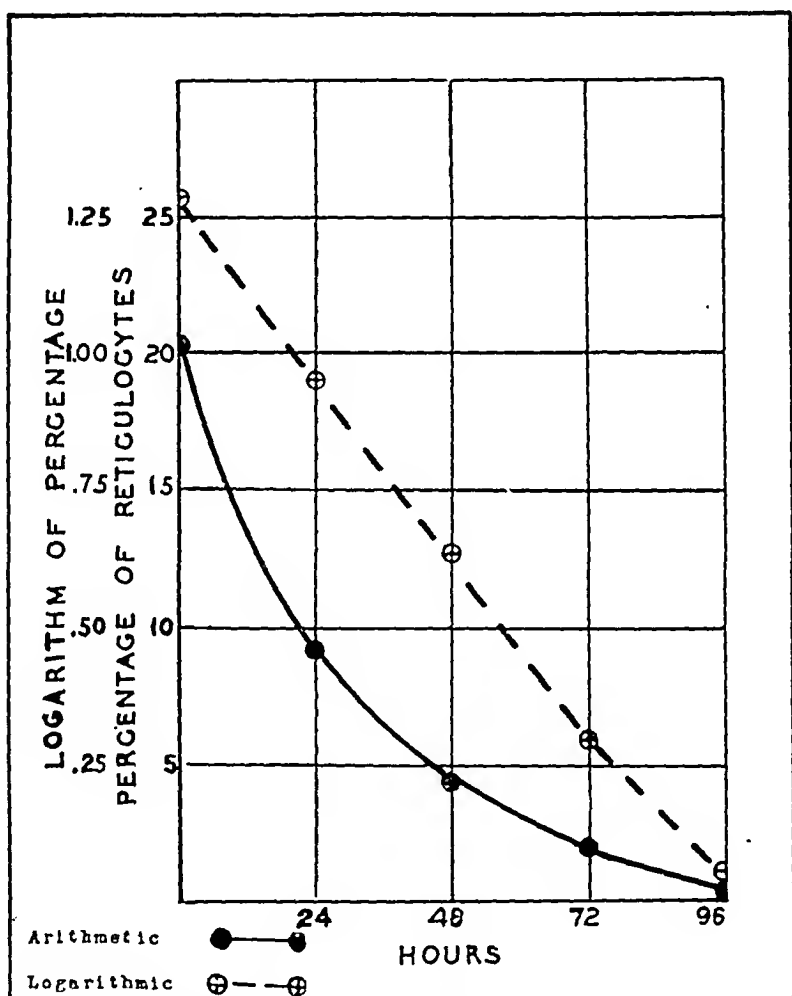


Fig. 1.—A typical example of the rate of decrease in the number of reticulocytes in vitro at 37 C. over a four day period.

ble. This decrease of reticulocytes at 37 C. is absolute as well as relative, because the total red blood cell counts remained constant within the limits of error during the first seventy-two hours. There is a variation in the rate of disappearance of these cells in the different experiments, but there is no fundamental difference to be observed between blood coming from different sources, e. g., between the rabbit and the human being, between bled rabbits and those into which injections of phenylhydrazine were made and between cases of hemolytic jaundice

drawn from the pleural cavity. Usually, after two or three days none of the injected blood could be obtained. Autopsy at this time revealed only a small amount of blood moistening the walls of the pleural cavity. The viscosity of this blood seemed much increased. Smears of the blood showed many large, vacuolated, phagocytic cells. The red blood cells were relatively uninjured, and the reticulocytes stained as well as after being in the incubator for several days.

Figure 2 illustrates the decrease of reticulocytes of the blood from a case of pernicious anemia (experiment 9, table 1). Samples were placed in the pleural cavity of a rabbit and at the same time in test tubes which were incubated at 37 C. The curves show a striking similarity between the decrease of reticulocytes in the incubator and that in the pleural cavity of the rabbit.

Five experiments of this nature were performed with rabbit's blood, with the result that the amount of reticulocytes decreased at a rate similar to that of reticulocytes in the incubator (table 1). No especial

TABLE 2.—*The Decrease of Reticulocytes at Room Temperature and in the Icebox*

Experiment	Temperature, C.	Percentage of Reticulocytes					
		Start	24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.	120 Hrs.
18	37	21.9	9.6	9.4	5.1
	23	22.4	20.1	21.0	23.0
21	37	30.3	18.6	14.8	4.8
	10	28.4	29.4	28.2	27.4	25.2	26.4

advantage of this method was demonstrated and it was abandoned. Phagocytosis of the red blood cells apparently was active in the pleural cavity, but reticulocytes were no more rapidly taken up than adult red blood cells. Evidence of phagocytosis in smears of blood from the test tube experiments has been observed only rarely.

THE DECREASE OF RETICULOCYTES IN VITRO AT TEMPERATURES LOWER THAN 37 C.

Similar test tube preparations of blood with a high reticulocyte count were kept in an icebox (10 C.) or at room temperature (23 C.) and observed over long periods. Reticulocytes could still be demonstrated at the end of six months when kept in the icebox. Pepper² observed reticulocytes in blood preserved in the icebox for one month, and under similar circumstances Key⁹ observed them for sixteen days.

In table 2 are recorded two of the numerous observations on rabbit's reticulocytes kept at temperatures lower than 37 C. There is no definite

9. Key, J. A.: Studies on Erythrocytes, with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch. Int. Med. 28:511 (Nov.) 1921.

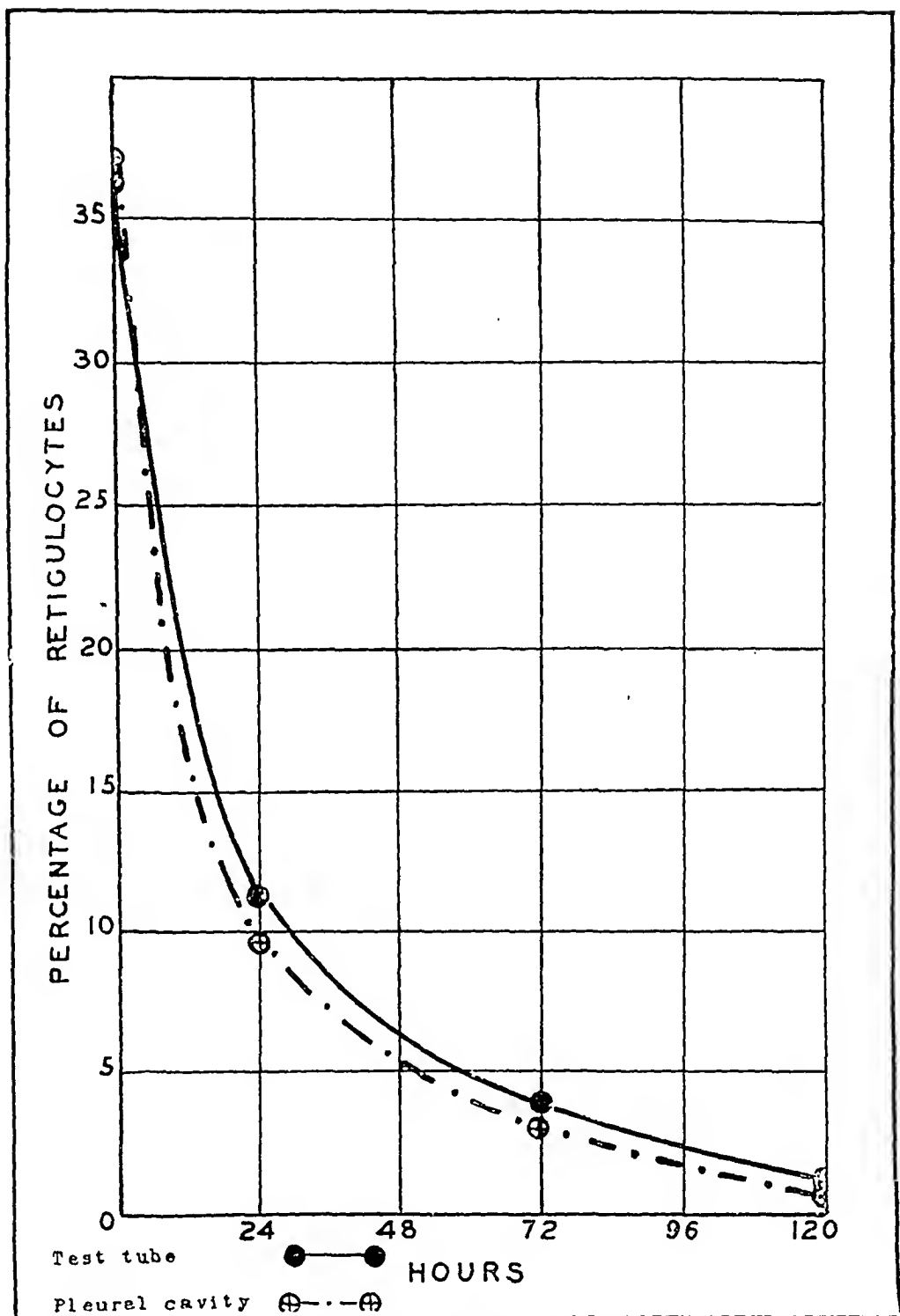


Fig. 2.—A comparison of the rate at which reticulocytes decrease in the test tube at 37 C. with the rate at which they decrease in the pleural cavity of the rabbit.

of red blood cells was proportionately much greater. These facts seem to indicate that slight hemolysis, such as occurred in some of the test tube specimens, is not a factor in influencing the results of these experiments. The discrepancies in the reticulocyte percentage decrease which occur after incubation for ninety-six hours may be due to extreme hemolysis.

A change in hydrogen ion concentration, which may accompany autolytic changes in incubated blood, perhaps may influence the reticulocytes. Gawrilow¹² found that slight changes in the hydrogen ion concentration affected the staining of reticulocytes by polychrome-methylene blue. This has not been found to be true for the method of staining reticulocytes used in this laboratory. Indicator tests of the p_H values of the supernatant serum after incubation of the blood for twenty-four and forty-eight hours have shown no significant change. Controlled experiments have been performed with cells in contact with large and small amounts of serum; this serum has been drawn off and replaced by fresh serum several times a day, without changing the rate at which the amount of reticulocytes decreased. Because of the possibility that there may be local changes about cells which rest compactly in the bottom of a test tube, blood has been automatically shaken in the incubator for several days, but this procedure also had no definite influence on the rate of decrease of reticulocytes. Cells placed in contact with buffer solution, salt solution and solutions of glycine, alanine or liver extract, which had different p_H values than serum, showed no constant difference in the rate of decrease of the amount of reticulocytes.

It appears, therefore, that the decrease in the number of reticulocytes in vitro is a phenomenon which occurs irrespective of degenerative changes taking place in blood in vitro.

THE TRANSFUSION OF RETICULOCYTES

A series of experiments was performed in which citrated rabbit's blood containing from 20 to 30 per cent of reticulocytes was transfused into normal rabbits. In all cases there was an immediate rise of the reticulocyte percentage in the peripheral blood, usually to more than twice the initial count, or from about 3 to 6 per cent. Within from twelve to forty-eight hours, the reticulocyte percentage dropped slowly toward the initial level. No dependable conclusion regarding the maturation rate of reticulocytes can be drawn from these experiments because the reticulocyte count of the rabbit varies considerably from time to time under normal conditions, and also because a relatively large

12. Gawrilow, R.: Zur Lehre über die vitalfärbbare Substanz der Erythrozyten, *Folia haemat.* **38**:216 (June) 1929.

evidence that there was any decrease over five or six days. Many of the reticulocytes developed small granules, taking the brilliant cresyl blue stain after being in the icebox for a few days. This phenomenon will be described presently. Lowering the temperature inhibits the decrease of reticulocytes which takes place so actively at 37 C.

THE RELATION OF THE DECREASE OF RETICULOCYTES TO DEGENERATIVE CHANGES OF BLOOD IN VITRO

Although hemolysis of the red blood cells was slight when blood was incubated for a few days and occurred much more slowly when blood was kept in the icebox, it is possible that the liberation of hemoglobin may have a significant influence on the decrease of reticulocytes in vitro. However, this seems unlikely. Pepper¹⁰ summarized the inconsistent statements in the literature concerning the fragility of reticulocytes, and he was unable to demonstrate that reticulocytes are more or less fragile to hypotonic salt solutions than adult red blood cells. There is no conclusive evidence that reticulocytes are more easily destroyed than non-reticulocytes, and, in fact, there is some evidence that at least under certain conditions they are more resistant.¹¹

In the pleural cavity of the rabbit, while active phagocytosis was taking place, it was observed that the reticulocytes of the injected blood decreased at a similar rate to those in the blood incubated in test tubes. Therefore, reticulocytes are no more easily destroyed by phagocytosis than adult red blood cells.

Whereas there is only a very slight trace of hemolysis in blood incubated for twenty-four hours, the greatest decrease of reticulocytes takes place during this period. Repeated red blood cell counts of the incubated specimens performed during the first forty-eight hours varied within the limits of technical error. After seventy-two hours there was a slight increase in the number of shadow cells seen in the counting chamber but these numbered only 2 or 3 per cent of the total count, whereas the decrease in the number of reticulocytes was of a much greater magnitude. If distilled water, up to 0.8 cc., was added to 1 cc. of whole blood, there was no definite decrease in the reticulocyte percentage in spite of definite hemolysis. When equal parts of distilled water and blood were mixed, there was about a 50 per cent reduction of the number of reticulocytes, but the reduction of the total number

10. Pepper, O. H. P., and Peet, M. M.: The Resistance of Reticulated Erythrocytes, *Arch. Int. Med.* **12**:81 (July) 1913.

11. Isaacs, R.; Brock, B., and Minot, G. R.: The Resistance of Immature Erythrocytes to Heat, *J. Clin. Investigation* **1**:425 (June) 1925. Minot, G. R., and Buckman, T. E.: Erythremia (Polycythemia Rubra Vera), *Am. J. M. Sc.* **166**:469 (Oct.) 1923.

Pepper² observed similar granules in rabbit's blood kept on ice. They undoubtedly are not the "chromatic granules" which he observed in moist preparations of incubated rabbit's blood and which he related to the "substantia metachromaticogranulosa" of Cesaris-Demel.¹⁴ The granules do not resemble Howell-Jolly bodies, or the nuclear particles described by Morris,¹⁵ and they cannot arise from the nucleus in bloods which contain very few or no nucleated erythrocytes. Dr. Raphael Isaacs examined some of the preparations showing these granules, and he stated that they were not identical with the granules described by him.¹⁶ They were seen in cells from cases of pernicious anemia at the height of the reticulocyte response following liver therapy. In a case of chronic familial hemolytic jaundice, 6 per cent of the red blood cells contained such granules. In the reticulocytes of blood incubated for forty-eight hours, these granules appear in the midst of the reticular substance; sometimes they are present in greater amount than the reticular substance itself.

The cells containing granules but not reticular substance (that is, strands or net forms staining with brilliant cresyl blue) were counted in blood incubated as usual for from three to four days. These counts were compared with the reticulocyte counts of the same preparations. Figure 4 gives data from a case of pernicious anemia in which a comparison is made between the number of cells containing granules only and the number of cells containing reticular substance. Whereas the number of reticulocytes decreased on incubation of the blood, the number of cells containing granules increased, and subsequently decreased at a slower rate than the reticulocytes. The maximum number of cells with granules appeared at different times in the experiments on three different days. The significance of this observation will be discussed later.

Similar but less pronounced results were obtained with rabbit's blood containing large numbers of reticulocytes. Normal human blood, with 0.6 per cent reticulocytes, showed only 0.3 per cent of cells with granules after seventy-two hours of incubation.

These granules resemble individually the granules in punctate basophilia and the nodal points of the reticular substance seen when stained with brilliant cresyl blue. Punctate basophilia is probably of the same

14. Cesaris-Demel: Studien über die roten Blutkörperchen mit den Methoden der Färbung in frischen Zustände, *Folia haemat.* 4:1 (Oct.) 1907.

15. Morris, R. S.: Nuclear Particles in the Erythrocytes, *Arch. Int. Med.* 3:93 (March) 1909.

16. Isaacs, R.: The Refractive Granule Red Blood Corpuscle: Its Behavior and Significance, *Anat. Rec.* 29:299, 1925.

error is introduced in counting reticulocytes when they are few in number. The influence of transfusion itself on the reticulocyte level is also a factor. The results of the experiments, however, are not inconsistent with the rate of decrease in the number of reticulocytes in incubated blood or in blood placed in the pleural cavity, and they indicate that reticulocytes injected into the circulation are not immediately withdrawn; for example, by phagocytosis or by some organ.

THE APPEARANCE OF GRANULES IN THE RED BLOOD CELLS

Small granules in many of the reticulocytes, and in cells free from reticular substance, have been observed in both human and rabbit blood, after incubation and after remaining in the icebox. These granules are more pronounced in the cells of the human blood that was studied than

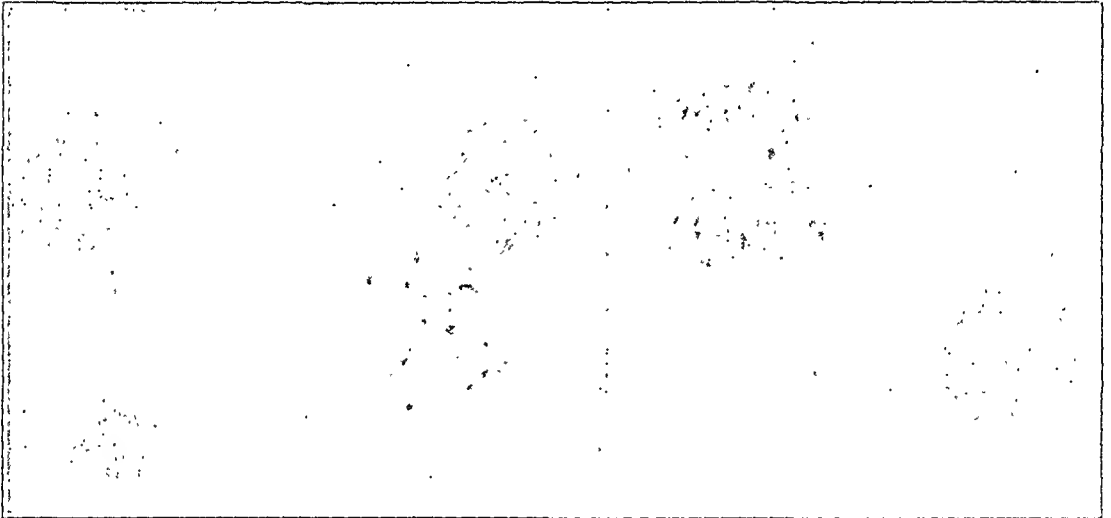


Fig. 3.—Basophilic granules in the red blood cells incubated at 37° C. for forty-eight hours. Wright's stain; $\times 2,200$. The blood was taken from a case of pernicious anemia at the peak of the reticulocyte response following liver therapy.

in the cells of the rabbit blood. In cells without reticular substance the granules number usually from one to twenty, and sometimes even more. They appear scattered through the cell; sometimes one or two may be at the periphery. These granules vary in size, are often irregular in shape and stain with brilliant cresyl blue and Wright's stain (fig. 3). Sometimes they appear as short rods resembling what Schilling¹³ has described as "erythrokanten." Basophilic rods resembling Schilling's "erythrokanten" have been observed in the unincubated blood from cases of pernicious anemia, hemolytic jaundice and purpura hemorrhagica.

13. Schilling, V.: "Erythrokanten," Stäbchen in Erythrocyten, bei Anaemia perniciosa und einigen nahestehenden Krankheitsbildern, *Klin. Wchnschr.* **7**:785, 1928.

occurs in vitro bears a close relation to processes of maturation in the blood stream.

It is exceedingly probable that younger reticulocytes contain larger amounts of reticular substance than older reticulocytes. The significance of different types of reticulocytes has been commented on by Lee, Minot and Vincent.¹⁸ Seyfarth and Jürgens⁴ studied the blood of mouse embryos and noted that with the increasing age of the embryos the number of red blood cells with a "thick, knotted form of substantia granulofilamentosa" diminished, while that of the cells with "speckled or net form" and cells without basophilic substance increased.

Gawrilow¹⁹ divided reticulocytes into cells of three ages: the youngest are those with heavily constructed reticular substance; an intermediate type is recognized, and the most mature cells are those with isolated threads or granules. In anemia produced in guinea-pigs by the injection of phenylhydrazine, he found that as the number of reticu-

TABLE 3.—*Types of Reticulocytes in a Case* of Pernicious Anemia During the Reticulocyte Response*

Time Relative to Peak of Reticulocyte Response	Cells Containing Reticular Substance		
	Cells with Large Amount, per Cent	Cells with Medium Amount, per Cent	Cells with Small Amount, per Cent
Two days before peak.....	28.5	54.0	17.5
Day of peak.....	13.0	64.0	23.0
Two days after peak.....	6.5	60.5	33.0

* Table 1, experiments 4, 5 and 6.

locytes increased they were mostly of the heavily constructed type; at the peak of the rise the majority were of the intermediate type; later, most of them contained only isolated threads or granules.

In several of the cases of pernicious anemia, before, during and after the reticulocyte response due to liver therapy, a quantitative differential count of the reticulocytes was made. The reticulocytes were classified according to three types, those having large amounts of reticular substance, medium amounts and small amounts. All three types are present at the same time, but early in the reticulocyte response more cells have large amounts of reticular substance, whereas later, more cells have small amounts of reticular substance. In table 3 are given the percentages of cells in each of these three classes from the blood of a patient with pernicious anemia two days before the peak of

18. Lee, R. I.; Minot, G. R., and Vincent, B.: Splenectomy in Pernicious Anemia, J. A. M. A. **67**:719 (Sept. 2) 1916.

19. Gawrilow, R.: Experimentelle Untersuchungen über das Verhältnis verschiedener Retikulozytenformen zueinander bei akuten Anämien, Folia haemat. **38**:246 (June) 1929.

nature as diffuse basophilia which manifests itself as reticular substance when stained supravivally by certain dyes. Many authors describe punctate basophilia as basophilic substance altered by the action of certain toxic substances such as lead.¹⁷ Because of the appearance of these granules in reticulocytes and their increase with the decrease of the reticulocytes, it is logical to conclude that they arise from or are a form of the basophilic substance of young red blood cells. Their presence in freshly drawn human blood containing large numbers of reticulocytes makes it probable that they appear *in vivo* in the course of the development of the red cell.

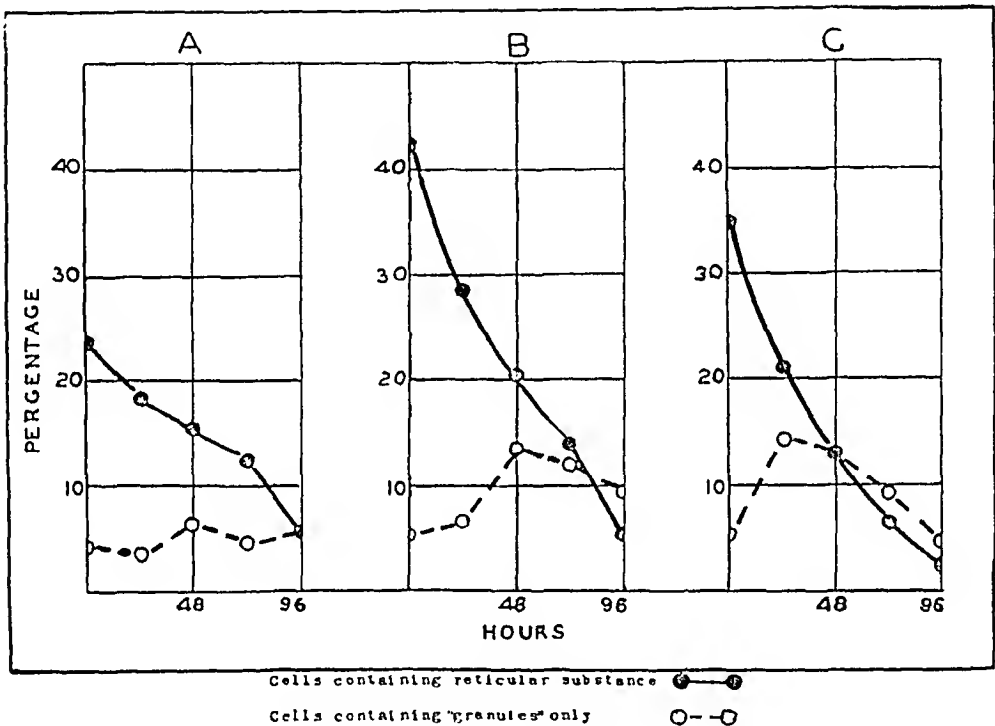


Fig. 4.—Progressive changes observed, *in vitro*, at 37 C. in the erythrocytes from a case of pernicious anemia during the reticulocyte response. *A*, two days before the peak of the reticulocyte response; *B*, at the peak of the reticulocyte response; *C*, two days after the peak of the reticulocyte response.

THE RELATION BETWEEN THE AGE OF THE RETICULOCYTES AND THEIR RATE OF DECREASE

Older cells should reach maturity in a shorter time than younger cells. If it can be shown that older reticulocytes decrease faster than younger reticulocytes in the incubator, the result will suggest that what

17. Pappenheim, A.: *Spezielle Morphologie und Genese der Blutzellen*, *Folia haemat.* **24**:110, 1919. Brookfield, R. W.: *Blood Changes Occurring During the Course of Treatment of Malignant Disease by Lead*, with Special Reference to Punctate Basophilia and the Platelets, *J. Path. & Bact.* **31**:277, 1928. Morawitz and Denecke (footnote 3). Gawrilow (footnote 12.)

the reticulocyte response, at the peak and two days after the peak. Figure 5 *A* shows the reticulocyte response of this patient and records at what three times the quantitative differential count of the reticulocytes was determined.

At the same times blood was also taken for incubation at 37 C. The rate of decrease of the reticulocytes in vitro was determined for each of the three days and is shown on figure 5 *B*. They decreased in vitro slowest when they were increasing in the peripheral blood, or when the majority of the cells had large amounts of reticular substance. Furthermore, they decreased fastest in vitro when the majority of the cells had small amounts of reticular substance, or when the number of reticulocytes in the patient's blood stream had begun to decrease. In addition, there seemed to be a definite relationship between the rate of decrease of reticulocytes in incubated blood and the rate at which cells containing granules increased (fig. 4).

TABLE 4.—*Three Types of Reticulocytes from Blood* of Patients with Pernicious Anemia in Vitro at 37 C.*

Period of Incubation at 37 C.	Cells Containing Reticular Substance		
	Cells with Large Amount, per Cent	Cells with Medium Amount, per Cent	Cells with Small Amount, per Cent
Start .	23.5	54.0	17.5
24 hours	12.5	59.0	28.5
48 hours	5.5	50.0	44.5
72 hours	4.0	51.0	45.0
96 hours	1.0	36.0	63.0

* Table 1, experiment 4

A similar quantitative division of the reticulocytes was performed on many bloods incubated at 37 C. During the period of incubation and while the total number of reticulocytes was diminishing, the percentages of reticulocytes containing large amounts of reticular substance decreased while those containing small amounts increased. Furthermore, while reticulocytes were disappearing from the blood in vitro the reticular substance of those remaining was changing to a more mature form. An observation of this sort is given in table 4.

If blood is centrifugated, the reticulocytes tend to accumulate in the top layers of cells. This knowledge was utilized to separate the less mature reticulocytes, that is, those containing large amounts of reticular substance, from the more mature reticulocytes or those containing small amounts of reticular substance.

Table 5 gives data which show that there is an accumulation of reticulocytes in the upper portion of a column of cells. In addition, there is a slightly greater percentage of reticulocytes containing large amounts of reticular substance in the upper than in the lower part of the centrifugated specimen. Studies of the rate of decrease in vitro of

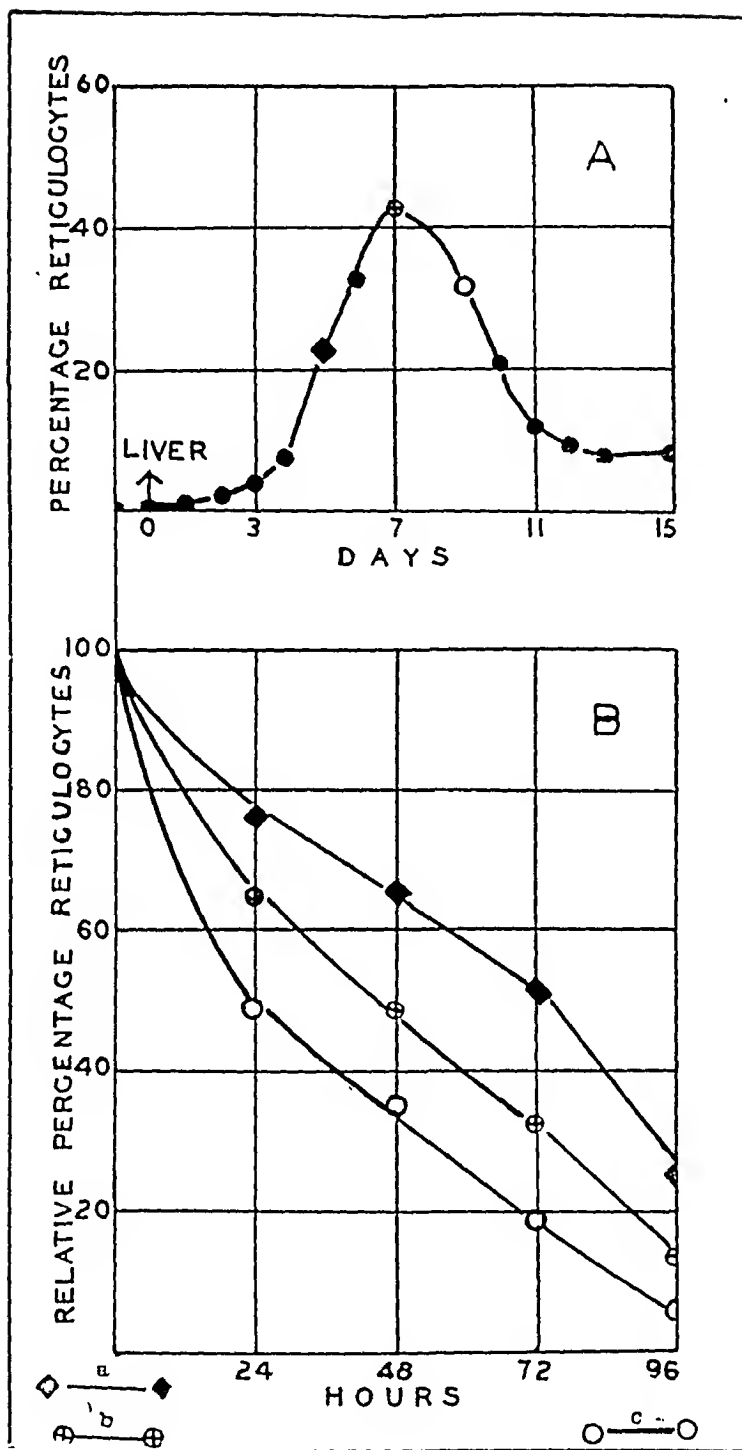


Fig. 5.—A study of the reticulocytes from a case (table 1, experiments 4, 5 and 6) of pernicious anemia during the reticulocyte response to liver therapy. Initial red blood cell count: 1,000,000 per cubic millimeter. *A* shows the percentage of reticulocytes in the blood of the patient following treatment. In *B* the blood from this patient, taken two days before the peak (*a*), at the peak (*b*) and two days after the peak (*c*), was incubated at 37 C. in test tubes. For purposes of comparison the initial level of the reticulocyte percentage for each experiment is considered as 100 per cent.

sooner and will be higher than if the same amount is divided into small doses which are fed over a long time. Further studies on the nature of reticulocytes in pernicious anemia under such varying conditions of response have been made and will be reported in a separate communication. Some of the results of these studies throw an interesting light on the problem of the life of reticulocytes and will be summarized here.

Varying grades of responses have been obtained in this clinic by the administration of experimental fractions of liver extract or of material the potency of which was to be tested. In a series of sixteen cases, in which the initial red blood cell level was between 1,000,000 and 2,000,000 per cubic millimeter, the reticulocytes were studied especially in relation to the amounts of reticular substance which they contained, or, in other words, in relation to their age. It was found that the reticulocytes in those cases which had a maximal response tended

TABLE 6.—*The Three Types of Reticulocytes in the Blood of Patients with Pernicious Anemia Two Days Before the Peak of the Reticulocyte Response to Liver Therapy: Maximal and Submaximal Responses*

Number of Cases	Percentage of Maximal Reticulocyte Response	Average Percentages of Cells Containing Reticular Substance		
		Cells with Large Amount	Cells with Medium Amount	Cells with Small Amount
4.....	17 to 45	7.0	58.4	34.6
4.....	100	20.8	58.4	20.8

to be of a considerably younger variety than those which had a submaximal response. This was especially true of the reticulocytes present two days before the peak and at the peak of the reticulocyte response. Table 6 gives the average figures of four cases which had a maximal response, and of four other cases which had a response of less than half the maximal. The maximal response for each erythrocyte concentration was estimated from data given by Minot and Cohn and their collaborators.²⁰

In one case in which a submaximal response was first obtained, and was followed later by a maximal response due to the feeding of a more potent material, the reticulocytes during the first response were more mature than those during the second response.

One case (that reported in table 1, experiments 4, 5 and 6) has been studied from many different angles and is of especial interest. This case, in which a maximal response was obtained, showed a prompt reticulocyte rise to a peak followed by a rapid drop to a low percentage in four or five days. The reticulocytes were studied in vitro at 37 C. by the usual technic. The rate of decrease in the absolute number

reticulocytes taken from the three layers of centrifugated blood show what is to be expected; namely, a slightly faster rate of decrease in the number of reticulocytes in the specimens containing particularly cells with smaller amounts of reticular substance than in those containing larger amounts of reticular substance.

These experiments seem to indicate a direct relation between the age of the reticulocytes and the period of time taken to reach maturity. In other words, reticulocytes probably reach maturity, or become non-reticulated erythrocytes, in a period of time depending on their age.

THE MATURATION OF RETICULOCYTES IN PERNICIOUS ANEMIA

The reticulocyte response in pernicious anemia following liver therapy has aroused a great deal of interest. The following question is to be answered: Do the reticulocytes which enter the circulation in great numbers develop into mature erythrocytes, or are they destroyed, for example, as foreign bodies?

TABLE 5.—*The Three Types of Reticulocytes in a Centrifugated Specimen of Blood*

Layer of Cells	Reticulocytes, per Cent	Cells Containing Reticular Substance		
		Cells with Large Amount, per Cent	Cells with Medium Amount, per Cent	Cells with Small Amount, per Cent
Top.....	38.4	28	49	23
Middle.....	9.4	21	51	28
Bottom.....	7.0	19	60	21

After the institution of liver therapy the reticulocytes usually begin to increase in number in from three to eight days and reach a maximum in the subsequent three to six days.²⁰ Minot and Cohn and their collaborators²⁰ suggested that the total erythrocyte increase up to the peak of the reticulocyte rise may be accounted for largely by the increase in these young cells. Following this, the total red cells count increases while the reticulocyte count decreases, probably because mature red cells are entering the circulation and because reticulocytes are maturing in the circulating blood.

The course taken by the reticulocytes after the institution of liver therapy depends somewhat on the amount and rate at which the active principle is administered and on the precise state of the given patient. Within certain limits, if large amounts of the active principle are fed, the reticulocytes rise to higher levels than if smaller amounts are fed. If a large amount is fed in a very short time, the response will come

20. Minot, G. R.; Cohn, E. J.; Murphy, W. P., and Lawson, H. A.: Treatment of Pernicious Anemia with Liver Extract, *Am. J. M. Sc.* **175**:599 (May) 1928. Cohn, Minot, Alles and Salter (footnote 5).

It has been demonstrated that reticulocytes have a definite oxygen consumption whereas adult erythrocytes have only a very slight oxygen consumption.²² There is, then, perhaps a direct analogy between the maturation rate of reticulocytes and the rate of senescence or death curve typical of many simple biologic and chemical phenomena. The development of the reticulocyte into the adult nonreticulated erythrocyte may be a true senescence or death. In favor of this is Denecke's²³ suggestion that the juvenile erythrocyte is not such a useful carrier of oxygen as the adult erythrocyte since it requires oxygen itself.

A problem of additional interest is the disposal of the basophilic substance which has disappeared from the young cell in the course of its maturation. It is probable that the basophilic substance diminishes gradually in amount as the cell reaches maturity. The observation of the increase of granules in erythrocytes with the decrease of reticulocytes suggests that this is a normal occurrence in the maturation of reticulocytes. The consumption of oxygen by the reticulocytes leads to the possibility of the disposal of the basophilic substance by normal catabolic processes.

It would be impossible to state definitely the duration of life of the reticulocytes in any one specimen of blood because of the many different ages represented. Reticulocytes containing large amounts of reticular substance probably mature into adult erythrocytes within from four to six days, whereas those containing small amounts of reticular substance probably mature into adult erythrocytes within from a few hours to several days. At all events, it seems evident that progressive changes toward senescence occur in the circulating reticulocytes.

CONCLUSIONS

1. Reticulocytes in vitro at 37 C. and in the pleural cavity of the rabbit decrease at a regular rate over a period of from one to four days. This rate is analogous to a death rate or a maturation rate.
2. The rate is similar for reticulocytes from various sources; for example, from bled rabbits, from those into which phenylhydrazine is injected and from cases of hemolytic jaundice and pernicious anemia.
3. The rate is much slower at 23 C. or at 10 C. than at 37 C. Reticulocytes have been found in blood kept in the icebox for six months.

22. Harrop, G. A., Jr.: The Oxygen Consumption of Human Erythrocytes, *Arch. Int. Med.* **23**:745 (June) 1919. Harrop, G. A., Jr., and Barron, E. S. G.: Studies on Blood Cell Metabolism: I. The Effect of Methylene Blue and Other Dyes upon the Oxygen Consumption of Mammalian and Avian Erythrocytes, *J. Exper. Med.* **48**:207 (Aug.) 1928.

23. Denecke, G.: Ueber den Stoffwechsel der Erythrozyten im anämischen Blute, *Deutsche med. Wchnschr.* **52**:280, 1926.

of reticulocytes in vitro corresponded remarkably closely to the rate of decrease which was observed in the patient. In other cases, however, the rate of decrease of reticulocytes was usually slower, but never faster, than was to be expected from the rate of decrease that was observed in vitro. This may be due to the fact that a small concentration of new, relatively mature reticulocytes enters the circulation following the peak of the reticulocyte responses.

In the same case the total number of new adult red blood cells which were present in the circulation one day following the peak of the reticulocyte response bore a close relation to the number of new adult red blood cells which could have been formed from maturing reticulocytes as determined by the experiments in vitro.

These observations are evidence that the life of reticulocytes in the circulation of patients with pernicious anemia is of a similar duration to the life of these young cells in vitro.

SUMMARY AND COMMENT

It has been shown that reticulocytes exist when incubated at 37 C. for from one to about five days. They remain for a very much longer time when kept in the icebox or at room temperature. That the reticulocytes lose their reticular substance and become adult erythrocytes is shown by the fact that the total number of red cells in the incubated specimens of blood does not diminish as the reticulocytes disappear. Evidence is presented to show that this must be the case in the blood stream, at least of patients with pernicious anemia at the time of the reticulocyte response following liver therapy.

It is never possible to do more than to assume that there is a direct analogy between in vitro and in vivo phenomena. By placing reticulocytes in the pleural cavity of rabbits, by the transfusion of reticulocytes and by observations on patients, an attempt has been made to reach conclusions based as nearly as possible on physiologic conditions. Whether the maturation of reticulocytes in the blood stream is the same as the maturation which takes place normally in great part in the bone-marrow is difficult to determine. A few reticulocytes are found in the circulation in health, and at birth considerable numbers are often present. It would be peculiar if they were destroyed as fast as they entered the circulation, when it is known that other cells of the bone-marrow—myeloblasts and myelocytes—may continue their growth in the circulation.²¹

21. Sabin, F. R.; Austrian, C. R.; Cunningham, R. S., and Doan, C. A.: Studies on the Maturation of Myeloblasts into Myelocytes and on Amitotic Cell Division in the Peripheral Blood in Subacute Myeloblastic Leukemia, *J. Exper. Med.* **40**:845 (Dec.) 1924.

Book Reviews

THE CHEST. By L. R. SANTE, M.D. Price, \$20. Pp. 500. New York: Paul B. Hoeber, Inc., 1930.

Under the caption "The Chest" the author has presented in semiatlas form the whole story of pulmonary disease from a roentgen standpoint. To the medical man not experienced in roentgen diagnosis its 500 pages of highly illustrated material may be used as an inductive study course which will stand the test of future experience. The experienced roentgenologist will find it an excellently classified review. The point of view of the author is excellent.

About 150 pages are first spent in describing and illustrating the physical basis for recognizing disease of the lungs by the roentgen rays. The following 250 pages make application of these principles to the great mass of pulmonary conditions most frequently encountered. The final 100 pages deal with the more rare or miscellaneous condition met with in the lungs, pleura, mediastinum and diaphragm.

The book is well balanced in that the major stress is placed on the commoner pulmonary inflammations, whereas only minor attention is paid to the unimportant and the bizarre.

PRAKTISCHE DIFFERENTIALDIAGNOSTIK FÜR AERZTE UND STUDIERENDE.
HERAUSGEGEBEN VON PROFESSOR DR. GEORG HONIGMANN. Band III:
Differentialdiagnostik in der Psychiatrie, von Hermann Haymann. Mit einem
Beitrag: Die diagnostische Bedeutung der Intelligenzprüfungen, von Erich
Stern. Price, 17 marks. Dresden, Theodor Steinkopff, 1930.

This work is a brief discussion of the important considerations in psychiatric differential diagnosis. Owing to the size of the book, each individual subject must necessarily be considered briefly. The contents are well organized and easily accessible through an adequate index. The same volume contains considerable worth while material in regard to intelligence tests.

The book is written and constructed for the use of general practitioners rather than for specialists in psychiatry, and seems to fulfil its purpose adequately.

4. The decrease in the number of reticulocytes is not related to degenerative changes which may take place in the blood in vitro.

5. No dependable conclusion regarding the maturation rate of reticulocytes can be drawn from the experiments on the transfusion of reticulocytes into rabbits, but the results are not inconsistent with the observations concerning their decrease in the test tube.

6. As the reticulocytes decrease in number in vitro, cells with "granules" progressively increase.

7. Reticulocytes having large amounts of reticular substance are less mature than those having small amounts of reticular substance and require a longer period of time to reach maturity.

8. There is an undoubted analogy between the rate of decrease in the number of reticulocytes in vitro and of those in the blood stream. In both instances this is probably true maturation. Evidence strongly in favor of this conclusion is given by studies on reticulocytes from the blood of patients with pernicious anemia during the reticulocyte responses following liver therapy.

in the four year period from January, 1926, to January, 1930, constitutes the source from which this report is made.

HISTORICAL DATA

The intracardiac route for the injection of drugs into the circulation received prominent attention at a symposium held in Munich in 1921. Guthman,² Vogt³ and Frenzel⁴ reported their experiences in the use of epinephrine injected into the heart when complete asystole developed during the course of surgical anesthesia. Up to that time, there had been collected from the literature twenty successful cases from seventy-six patients who had been treated by this method.

Prior to 1921, there were isolated reports in regard to the intracardiac route of injection; Vanden Veldin⁵ is said to have used this method as early as 1909. Fantus⁶ said that the German physiologist Schiff discovered this method of approach to the failing heart more than fifty years ago.

Boden,⁷ in 1923, had collected ninety cases with favorable results reported in twenty-three; most of these patients had received intracardiac injection of epinephrine for asystole of the heart occurring during operative procedures performed under general anesthesia. The literature since that time contains more and more reports of intracardiac injections used for resuscitation of the stopped heart.

Meyer,⁸ Raeschke,⁹ Petzetakis,¹⁰ Garipuy and Mériel,¹¹ O'Donovan and Fitzpatrick¹² and Sellheim¹³ contributed observations made during the attempt to reanimate the asystolic heart by the injection of epinephrine into the circulation. The success of their efforts led to an investigation into its possible use for the development of the circulation in stillborn infants. In 1926, Wachenfeldt¹⁴ and Bardier¹⁵ were able to resuscitate new-born infants when all other measures had failed; the injection of epinephrine directly into the heart met with favorable results.

2. Guthman, C.: München. med. Wchnschr. **68**:729 (June 17) 1921.

3. Vogt, E.: München. med. Wchnschr. **68**:732 (June 17) 1921.

4. Frenzel, B.: München. med. Wchnschr. **68**:730 (June 17) 1921.

5. Van den Veldin, quoted by Vogt, E.: München. med. Wchnschr. **68**:732, 1921.

6. Fantus, B.: The Technic of Medication, J. A. M. A. **87**:563 (Aug. 21) 1926.

7. Bodon, C.: Lancet **1**:586 (March 24) 1923.

8. Meyer, C.: Jahrb. f. Kinderh. **107**:76 (Sept.) 1924.

9. Raeschke, G.: Zentralbl. f. Chir. **51**:1628, 1924.

10. Petzetakis, M.: Presse méd. **34**:84 (Jan. 20) 1926.

11. Garipuy and Mériel: Presse méd. **34**:180 (Feb. 10) 1926.

12. O'Donovan, J. S., and Fitzpatrick, J. D.: Brit. M. J. **2**:524 (Sept. 18) 1926.

13. Sellheim, H.: Med. Klin. **22**:1323 (Aug. 27) 1926.

14. Wachenfeldt, M.: Monatschr. f. Geburtsh. u. Gynäk. **72**:185 (Feb.) 1926.

15. Bardier, E.: Bruxelles-méd. **8**:1242 (July 22) 1928.

RESUSCITATION OF THE STOPPED HEART BY INTRACARDIAC THERAPY*

ALBERT S. HYMAN, M.D.

Director, Witkin Foundation for the Study and Prevention of Heart Disease,
Beth David Hospital

NEW YORK

No procedure in modern medicine has aroused more controversial thought than the attempt to revive the dead. Hailed on the one hand as a miracle of science and on the other as a useless and dangerous operation,¹ the intracardiac injection method of resuscitating the stopped heart has occupied a stage of excited debate.

The dramatic circumstances attending the revival of those supposedly dead readily lends itself to exploitation by both the lay and the medical press. The subject is naturally one of appealing interest, touching as it does on two fundamental concepts of philosophic thought—life and death.

The increasing use of epinephrine for intracardiac injection in emergency conditions arising in the operating room and in the physician's office has been attended with such inconstant results that many surgeons and physicians are at a loss in evaluating the efficacy of this procedure, individual experience having rendered them either enthusiastic advocates or bitter opponents of this method of resuscitation.

In spite of the frequent isolated reports rendered by many authors who have published results of cases in which the patients were treated by intracardiac therapy, the literature contains no systematic study of this problem, and the physician is left confused and not a little bewildered by the loosely worded speculative thought which is often expressed in these cases.

Sensing the need of scientific inquiry into all phases of intracardiac therapy, the Witkin Foundation in 1926, created a special committee to investigate this problem. Through the philanthropic magnanimity of Mr. Witkin, funds were made available for the study of the various questions arising in the procedure of intracardiac manipulation. A correlation of results obtained from the laboratory, clinic and hospital

* Submitted for publication, Feb. 14, 1930.

* Published by permission of Grant No. 21 from the Witkin Fund.

* Report of the Special Committee on Intracardiac Therapy of the Witkin Foundation.

1. Editorial: Resuscitation and Intracardiac Injections, J. A. M. A. **94**:107 (Jan. 11) 1930.

tion. Other substances, when injected into the myocardium of such laboratory heart preparations will also cause a renewal of rhythm after standstill.

In attempts to resuscitate the stopped heart, injections into the pericardial cavity apparently have not been made intentionally. This, however, has been done inadvertently several times during attempts to inject substances into the heart. Failure to use needles of sufficient length, incorrectly placed needles and injections made before the needle had passed into the heart itself have been responsible for the injection of substances into the pericardial cavity. Neureiter¹⁶ had an opportunity to examine several subjects that had received "intracardiac injection" in the attempt at resuscitation; at the postmortem table he found that the injected material was in the pericardial cavity in two cases, and from a pathologic point of view no specific reaction could be discovered. Apparently, the injection of substances into the pericardial cavity has little or no effect on the heart at standstill.

A review of these facts would thus tend to indicate that as far as resuscitation is concerned, the procedure of injection into the heart seems to be most effective when the drug is placed in the heart muscle; it is very much less effective when injected into the cavities of the heart, and it apparently has no value when injected into the pericardial cavity.

DRUGS USED IN INTRACARDIAC INJECTIONS

While epinephrine has enjoyed widespread use as the drug *par excellence* for use in cardiac standstill, many authors have shown that this substance may not be used without great danger. Johnson and Siebert¹⁷ demonstrated that severe myocardial damage occurred in nearly all of their forty-seven animals that had been used in the study of this problem. Hume,¹⁸ Smirnow,¹⁹ and Lucchetti²⁰ have also shown that there may be extensive cardiovascular involvement following the use of epinephrine, more especially when it is injected during anesthesia. Neureiter¹⁶ confirmed many of these observations from autopsy material.

Many other drugs have been used for the resuscitation of the arrested heart. Bolton²¹ was successful in restoring contraction of the heart by the intracardiac injection of ether; in his case, the heart

16. Neureiter, F.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **12**:151 (Aug. 27) 1928.

17. Johnson, S., and Siebert, W. J.: Am. Heart J. **3**:279 (Feb.) 1928.

18. Hume, W. E.: Quart. J. Med. **21**:459 (July) 1928

19. Smirnow, A. J.: Ztschr. f. d. ges. exper. Med. **57**:554, 1927.

20. Lucchetti, Prat. méd. franç. **6**:113 (March) 1927.

21. Bolton, N. H.: Brit. M. J. **2**:482 (Sept. 11) 1926.

Within the past three years, there have been reported sixty-two other cases in which the intracardiac injection method of resuscitation has been employed; these reports, together with those previously mentioned, make a total of about 250 cases in about 25 per cent of which a favorable outcome was experienced.

WHAT IS MEANT BY INTRACARDIAC INJECTION

A brief study of the cases reported by various authors quickly reveals the great confusion existing in regard to the procedure called "intracardiac injection." With the exception of obscure references made in regard to the left ventricle, few investigators have even attempted to indicate specifically which part of the heart or adjacent structures they were attempting to reach by the injecting needle.

From a purely anatomic point of view, there are three sites that can be considered in the all-inclusive phrase "intracardiac injection": (1) the pericardium, (2) the wall of the heart and (3) the cavities of the heart.

Of these three sites, the attempt to inject substances into the cavities of the heart, and especially that of the left ventricle, was apparently the intent of many authors. The rationale of this thought seems to be based on the theory that with the heart at standstill the intravenous route of medication is ineffective, but if the injected drug reaches the heart immediately, it may be carried without delay to the easily perishable centers of the brain. Furthermore, injection directly into the left ventricle saves the time required for passage through the lesser circulation and hence enhances the chances of the injected material to reach the brain and other "vital centers" more quickly.

A consideration of this conception of intracardiac therapy would seem to show, however, that it is based on a fallacious theory; it is obvious that if the heart is at a standstill there will be no more circulation within the cavities of the heart than there will be in the venous or arterial circulation. One cannot accept the favorable results noted in resuscitation of the asystolic heart on the fact that the injected drug is placed more quickly into circulation.

Injection of the drug into the wall of the heart has been the intent of several more careful observers. Their conception of the process is based on certain facts demonstrable in the experimental laboratory; the isolated mammalian heart may be stimulated to automatic contraction after a period of standstill when epinephrine and other substances are injected into the myocardium. The local effect of epinephrine on the heart muscle has been widely studied by many investigators; the increase in the capillary circulation makes possible a quicker metabolic exchange in the myocardial fibers with a resulting renewal of automatic contrac-

gencies for at least the past seventy-five years, and the literature contains many reports of the favorable results obtained by this method.

When the emergency has developed during the course of a laparotomy, the surgeon has attempted to massage the heart by direct pressure on the diaphragm; squeezing, pinching or otherwise mechanically irritating the heart to recontract has been the theory behind such procedures (Cook²⁷). Indirect methods of cardiac massage by pressure applied on the thorax have often been resorted to. Krantzfeld²⁸ recently reviewed the various methods of mechanically stimulating the heart in such cases. Many devices and machines have also been devised to accomplish the same purpose.

Condorelli²⁹ described a case in which he kept the heart beating for more than two hours by thumping on the precordium; every time the heart was percussed a contraction occurred, but when the percussion was stopped the heart would immediately cease contracting, and the patient would become unconscious and moribund. The impossibility of continuing this procedure resulted in the death of the patient.

Eisenmenger³⁰ described a pumping apparatus which is applied to the abdomen; this device consists of a small motor which alternately massages the abdomen while a pump forces sodium chloride solution into the blood vessels. With this machine he was able to maintain a circulation in patients who had died; if the apparatus was used not more than ten minutes after cardiac standstill, favorable results might be expected. The machine, however, is so complicated that it has been difficult to make use of it clinically; Eisenmenger has therefore been devoting his attention to demonstrating the chemical changes that take place in the body during the time that artificial circulation has continued. His picturesque description of corpses that regain natural color and bodies that continue to show automatic movements has recently challenged the credulity of all Europe.

While the mechanical methods of resuscitating the asystolic heart still enjoy considerable vogue, the widespread attention given to the intracardiac injection procedure has made the latter method the one more widely used at the present time, so that the reports now appearing in the literature are concerned less and less with the mechanical theory of reanimating the stopped heart.

27. Cook, L.: *Brit. M. J.* **2**:1118 (Dec. 11) 1926.

28. Krantzfeld, I.: *Klin. Med.* **5**:808 (Aug.) 1927.

29. Condorelli, L.: *Minerva M. J.* **8**:343 (Aug. 18) 1928.

30. Eisenmenger, R.: *Trials with Mechanical Artificial Breathing* (Letter), *J. A. M. A.* **94**:121 (Jan. 11) 1930.

responded promptly to the injection when all of the usual methods of reanimation had failed.

Caffeine has been used with favorable results by several investigators. Bianchetti²² injected relatively small amounts in his case, while Wiechowski²³ tried huge doses of the drug; both authors were equally enthusiastic about its immediate action in moribund patients, one of them having been dead for about twelve minutes.

Dextrose was first used by Imerman;²⁴ he injected 10 cc. of a 20 per cent solution of dextrose directly into the heart of a patient suffering from insulin shock. With the patient apparently dead, the response to the intracardiac injection was prompt, and subsequent recovery occurred rapidly.

Sodium thiosulphate was utilized in an attempt to save a patient who had tried to commit suicide by taking a large amount of potassium cyanide; with the patient moribund, Zimman²⁵ injected this chemical directly into the left ventricle, with a favorable outcome. He reported no untoward results from the injection.

Many combinations of substances have also been used for intracardiac injection; Ronzini's solution²⁶ is probably the best known of this group. This solution contains epinephrine, atropine, pituitary extract, and lobeline and is injected in doses of from 2 to 4 cc.

Camphor, digitalis, strophanthin, metrazol, coramin, strychnine and hypertonic salt solution, either alone or in combination with each other and epinephrine, have been used for intracardiac injection. Vogt³ studied the effect of many of these substances, and his conclusion seemed to be that all of them are more or less valuable for resuscitation of the asystolic heart.

The wide variety of substances used for intracardiac injection suggests that the response of the heart is probably not specific to any pharmacodynamic action, but that other factors, to be discussed later, are responsible for the resuscitation of the heart.

MECHANICAL STIMULATION OF THE HEART

Accidental standstill of the heart is not an unfamiliar occurrence in the surgical amphitheater; this unfortunate experience can be related by every practicing physician. The attempt to resuscitate the heart by direct or indirect manipulation has been practiced during such emer-

22. Bianchetti, C. F.: *Riforma med.* **42**:498 (May 24) 1926.

23. Wiechowski, W.: *Wien. klin. Wchnschr.* **41**:475 (April 5) 1928.

24. Imerman, S. W.: Intracardiac Injection of Dextrose in a Case of Insulin Hypoglycemia, *J. A. M. A.* **89**:1778 (Nov. 19) 1927.

25. Zimman, J.: *Semana méd.* **1**:1235 (May 17) 1928.

26. Ronzini, M.: *Policlínico* **35**:90 (Feb. 15) 1928.

Sufficient facts are at hand, however, to indicate that some attempt should be made to reestablish cardiac activity even if there has been a long period of cardiac arrest; if the procedure of injection is performed in the manner to be described later, a favorable outcome may be expected in cases in which the patients might otherwise have succumbed.

INDICATIONS FOR INTRACARDIAC INJECTIONS

Any procedure fraught with so many sequela, both good and bad, must be intelligently understood before its performance is undertaken; a consideration of the use of intracardiac injections must be made to determine the indications and contraindications in its selection as a method of resuscitating the stopped heart. Widespread utilization and poorly selected cases have done much to discredit this mode of reanimating the asystolic heart.

As long ago as 1924, Meyer⁸ suggested that all hearts in which cardiac arrest has occurred could be divided into two groups: (1) the healthy asystolic heart and (2) the heart in acute or chronic disease.

In the first group may be placed the heart that stops under narcosis, anesthesia, shock, accidents, injuries and collapse; while in the second group may be placed hearts suffering from those cardiovascular conditions leading to or associated with decompensation or general vasomotor breakdown. To the second group Vogt³ added arterial sclerosis, muscular degeneration of the heart, hyperthyroid disease with cardiac complications and nephrosis. Van den Velden⁵ thought that collapse from the acute infectious diseases should be considered; Hesse³⁵ suggested the incorporation of peritonitis from perforations, epidemic meningitis, diphtheria, pneumonia, pulmonary tuberculosis, typhus and typhoid. Finally, Blau³⁶ added poisoning by chemicals or gases.

A review of these conditions suggests that intracardiac injection should be more effective in the first than in the second group. There can be no question that when the heart is normal and unaffected by disease process in itself or in other parts of the body, the efficacy of this method of resuscitation must be much better than in the other group. This is readily borne out by an analysis of the successful cases that have been reported in the literature; most, if not all, of these have been made of cases appearing in the first group. The unsuccessful and poor results have been found almost exclusively in the second group, and it has been in the latter group that most of the serious complications, like hemopericardium, pericardial infection, embolism and general septicemia, have occurred.

35. Hesse, quoted by Meyer, C.: *Jahrb. f. Kinderh.* **107**:76 (Sept.) 1924.

36. Blau, J., quoted by Meyer, C.: *Jahrb. f. Kinderh.* **107**:76 (Sept.) 1924.

THE RESUSCITATION PERIOD

Physiologists have long maintained that a sudden stopping of the circulation results in an unequal response on the part of different tissues of the body. Certain centers of the brain are apparently quickly effected, while simple glandular structures like those of the hair follicles in the skin have been demonstrated to exhibit signs of activity even seventy-two hours after the heart has stopped beating. The easily perishable centers of the brain, however, are said to be irreparably damaged after from five to eight minutes of cerebral anemia.

The question as to how long asystole of the heart may exist and yet be responsive to intracardiac therapy apparently bears no relation to the physiologic thought previously expressed. Many cases of cardiac arrest have been reported which have greatly exceeded the maximum of eight minutes laid down by the experimental physiologist.

The period during which resuscitation may be possible has been found by different authors to be as long as from fifteen to twenty minutes, the longest case being that reported by Truzzi,³¹ in which a man, aged 70, was effectively treated by intracardiac injection more than half an hour after all signs of cardiac activity had ceased. Kleinberg³² recorded a case in which the patient was successfully treated twenty minutes after standstill of the heart; his patient was unquestionably dead before intracardiac therapy was resorted to. Johnson's³³ patient was a child, who was resuscitated twelve minutes after apparent death; Lutand's³⁴ patient recovered after ten minutes of cardiac standstill.

To these cases may be added two of our own; one, that of a man, aged 36, with cardiac arrest while on the operating table. Epinephrine injected into the heart eleven minutes afterward caused prompt recovery. The other case was that of a child who suffered from asystole of the heart during tonsillectomy; fourteen minutes after apparent death, 3 cc. of metrazol was injected into the left ventricle with a favorable result, the child showing no untoward results.

To describe the interval during which restoration of cardiac activity may be possible, we have used the phrase "resuscitation period." This period seems to be much longer than that previously conceived, and further experimental study is required to determine what its actual duration may be in relation to the various factors of age, sex, anesthesia, shock, hemorrhage and disease.

31. Truzzi, E.: *Gazz. d. osp.* **49**:1507 (Nov. 25) 1928.

32. Kleinberg, S.: *Pulmonary Embolism Following Oxygen Injection of a Knee*, *J. A. M. A.* **89**:172 (July 16) 1927.

33. Johnson, G.: *Norsk mag. f. laegevidensk.* **89**:478 (May) 1928.

34. Lutand, P.: *Bull. et mém. Soc. de chir. de Paris* **20**:874 (Dec. 21) 1928.

Injections into the cavities of the heart appear to rank in effectiveness about half way between these two.

4. The procedure is more successful in the normal asystolic heart (group 1) than in hearts suffering from disease processes (group 2).

5. While epinephrine has been used most often, there is a wide selection of drugs that has proved to be effective in the resuscitation process.

6. The resuscitation period apparently bears no relation to the time limits of hazardous cerebral anemia set down by the experimental physiologist.

7. Little or no damage is suffered by the myocardium if the operation of intracardiac injection is performed with the same care and skill exhibited in any other sterile surgical puncture.

8. Many cases have been reported in which resuscitation has been successfully brought about, only to have the patient collapse suddenly and die a few minutes or hours afterward without apparent cause.

9. In properly selected cases, such as those in group 1, a favorable outcome may be expected in about 25 per cent of patients who are apparently dead when treated by the intracardiac injection method.

A NEW CONCEPTION OF RESUSCITATION OF THE STOPPED HEART BY INTRACARDIAC METHODS OF TREATMENT

In considering the large and varied number of substances successfully utilized in intracardiac injection for reanimation of the stopped heart, it appeared to us that the response of the heart was not specific for any one chemical substance. The single constant factor in each injected substance was apparently its irritant action, and this action is effective only as far as the muscle of the heart alone is concerned. When the same drug was injected into the pericardium no effect was noted, while injection into any of the chambers of the heart was only moderately successful.

Closer scrutiny of all of the facts in the problem emphasized the differences seen in the reaction to the injection operation exhibited by the hearts of the two groups discussed before, wherein the normal asystolic heart of group 1 can be more readily stimulated to recontraction than the pathologic heart of group 2.

There is abundant clinical and experimental evidence to show that the asystolic heart of group 1 can be resuscitated by simple mechanical irritation. Condorelli's case²⁹ is a splendid example of this; each tap on the precordium elicited a pulse beat at the wrist. Korbler's experiments³⁸ on rabbits showed that while intracardiac injections did little or

38. Korbler, G.: *Arch. f. klin. Chir.* **150**:115, 1928.

Intracardiac injection should be reserved, therefore, with few exceptions, for the normal healthy heart that has stopped for the reasons enumerated in group one. To these, however, may be added another group of conditions occurring in childhood and infancy which seem to be peculiarly responsive to this method of therapy—asphyxia of the newly born or premature infant, thymic death and collapse from chronic nutritive disorders.

Occasionally, intracardiac therapy may be indicated in serious decompensation of the heart when all other methods of administering drugs are ineffective. Schultze³⁷ reported a case in which a girl, aged 7 years, was given fifteen intracardiac injections of strophanthin with successful results. We have used a digitalis product by the intracardiac route three times with a favorable outcome in one case.

In selecting cases for intracardiac injection in the hope of restoring cardiac activity, attention must thus be paid to the general condition of the patient. When the patient is suffering from serious systemic disease and when the heart has stopped as the result of myocardial degeneration, it is obvious that such cases are unsuited for intracardiac attempts at resuscitation; failure will be the rule.

On the other hand, when a patient is undergoing a surgical operation or when shock and injury have rendered an otherwise normal person moribund as the result of cardiac arrest, the intracardiac mode of stimulating automatic contraction of the heart should be attempted, as this procedure offers a favorable outcome if performed in a satisfactory manner.

PRESENT STATUS OF INTRACARDIAC THERAPY FOR RESUSCITATION OF THE STOPPED HEART

From the foregoing data, the present status of intracardiac injection for reviving the stopped heart may be summarized briefly as follows:

1. A sufficiently large number of persons have been resuscitated after apparent death by the use of intracardiac injections to make this method worthy of further study.

2. Considerable confusion exists in regard to the procedure called "intracardiac injection," little if any attempt being made to determine the actual site of the injection—whether pericardial, myocardial or into the chambers of the heart itself.

3. From an experimental point of view, the procedure is unquestionably more effective when the drug is injected into the heart muscle alone, and least effective when it is placed in the pericardial cavity.

37. Schultze, M., quoted by Meyer, C.: *Jahrb. f. Kinderh.* **107**:76 (Sept.) 1924.

myocardium have been grossly disturbed, the puncture wound made by the injecting needle may initiate a series of extrasystoles that occur so rapidly that ventricular fibrillation supervenes with immediate collapse of the heart and death.

This is what probably happens in the cases mentioned in section 8 under the heading "Present Status of Intracardiac Therapy for Resuscitation of the Stopped Heart," in which resuscitation has occurred and the heart has commenced to beat again, only to stop suddenly within a few moments or hours. Liang's⁴¹ patient lived for five hours after intracardiac injection and then "the circulation collapsed"—an apt description.

More accurate observers have suggested that the "second death" has been the result of ventricular fibrillation (Smith⁴²). In a case of complete heart block with unconsciousness due to the Stokes-Adams syndrome, Levine and Matton⁴³ noted a period of ventricular fibrillation following the intracardiac injection of epinephrine; their patient made a favorable recovery, due, perhaps, to the peculiar pathologic changes occurring in auricular and ventricular dissociation.

Opportunity for the clinical demonstration of the mechanical irritation theory of resuscitation of the stopped heart has been afforded in two cases, the first of which is presented here. A boy, aged 12 years, suffered from cardiac collapse while under anesthesia; after all other methods of resuscitation had failed, a long needle was inserted into the left ventricle. The heart contracted promptly, and the patient made an uneventful recovery. No drug was injected, although a syringe containing epinephrine had been prepared for use if the experiment failed. In this case, the mere prick of the needle was apparently enough to start automatic contraction of the heart.

The success of this demonstration led us to a further study of the extrasystolic arrhythmias, in an attempt to develop measures for the prevention of ventricular fibrillation and secondary collapse of the heart after resuscitation.

When the ectopic focus of extrasystoles lies in the auricles, the ventricular response is normal in all respects, with the sole exception of its prematurity. The ventricular rate may be very rapid, but the protecting mechanism provided by the junctional tissue and bundle system tends to reduce or filter out many of the stimuli; physiologic block develops and the ventricle beats slower. This is seen clinically in rapid auricular flutter or paroxysmal auricular tachycardia, in which the auricular con-

41. Liang, P. K.: *Brit. M. J.* **2**:1176 (Dec. 18) 1926.

42. Smith, G. F. R.: *Brit. J. Anesth.* **4**:207 (April) 1927.

43. Levine, S. A., and Matton, M.: *Heart* **12**:271 (March) 1926.

no damage to the myocardium, sometimes a puncture wound alone would reactivate a stopped heart.

With this thought in mind, it occurred to us that the success of the intracardiac injection theory of resuscitation depended more on the puncture of the heart by the injecting needle than on the substance injected.

The truth of this statement is easily verified. If one returns for a moment to a consideration of cardiac physiology, it can be demonstrated that while the heart is made up of specialized mechanisms, each part of the heart retains some vestige of a common embryologic tissue in which the factors of irritability, conductivity, contractility and stimulus production may be latent. In a recent textbook on electrocardiography,³⁹ we pointed out the teleologic significance of this observation as a potential life-saving mechanism when the orderly sequential phenomena of the cardiac cycle are disturbed.

When such disturbances occur, any myocardial fiber may assume the rôle of the pacemaker of the heart; any point that temporarily becomes more irritable than the sino-auricular node may initiate a stimulus for contraction of the entire heart. This is, in brief, the current theory of the extrasystolic arrhythmias of the heart.

When such a point of irritability becomes effective, it occurs before the normal pacemaker has an opportunity to discharge its impulse for the cardiac cycle and a premature beat occurs. If, however, the pacemaker is unable to release its stimulus, some other part of the auricle may become irritable and excite the heart to contract, or the atrio-ventricular node of Tawara may assume the rôle of the pacemaker.⁴⁰

Thus, nature has attempted to prevent standstill of the heart by providing other mechanisms for stimulating contraction. The myocardium of the normal heart at standstill tends to become very irritable and responsive to any stimulus that is intensive enough to initiate discharge of the electrodynamic factors necessary for contraction of the heart muscle.

This explains the mechanism of resuscitation of the stopped heart by intracardiac injection; the prick of the needle alone may be, and usually is, sufficient to initiate the stimulus required for contraction.

In carefully controlled experiments it can be demonstrated that the first beats of the resuscitated heart are extrasystoles. If the heart has not been too badly damaged by the period of anoxemia through which it has passed during asystole, a normal sinus rhythm may be promptly instituted. On the other hand, when the irritability factors of the

39. Parsonnet, A. E., and Hyman, Albert S.: *Applied Electrocardiography*, New York, The Macmillan Company, 1929, p. 75.

40. Hyman, Albert S.: *Postinfluenzal Bradycardia*, *Arch. Int. Med.* **40**:120 (July) 1927.

danger of penetrating the great vessels, as they lie at least 3 inches (7.6 cm.) above and below this level.

The clinical demonstration of this method of approach to the right auricle was attempted in four cases in which the patients had died as the result of various ailments; the first two had died of pneumonia. Injection into the right auricle was attempted after mere penetration had failed to elicit cardiac activity; no result was obtained. The third case was that of a woman who had died of general carcinomatosis; insertion of the needle into the right auricle in this case was followed by weak, irregular contractions of the heart after there had been complete cardiac standstill for about nine minutes. The heart continued to beat for about seventeen minutes, and then all sounds disappeared.

Results in the fourth case were especially gratifying. The patient, a woman, aged 45, who was suffering from mitral stenosis and with severe decompensation, succumbed to a complete collapse after having had several sinking spells during the previous twenty-four hours. Seven minutes after she had been pronounced dead by the intern on service, a needle was inserted into the right auricle. There was an immediate response on the part of the heart; a very rapid, irregular rate suggesting auricular fibrillation occurred. The needle was quickly withdrawn and in about an hour the patient began to show voluntary movements, although still semiconscious. At this time an intravenous injection of strophanthin and dextrose was given, and after a rather stormy six hour period she became conscious and could speak to those around her. This patient lived for about eight days, finally dying of her cardiovascular disease. No attempt was made to resuscitate her the second time.

To these four cases, which properly belong in group 2 and therefore cannot be considered as suitable for this method of resuscitation, may be added the case of a patient who suffered from cardiac standstill following the manipulation of a fractured femur. The patient was a man, aged 31, who collapsed under anesthesia while the surgeons were attempting reduction. As artificial respiration proved futile, a needle was inserted into the right auricle about six minutes after cardiac arrest. After a very short interval, heart sounds were heard and in about ten minutes the pulse was easily palpable at the wrist and running regular at a rate of 88. The patient made an uneventful recovery.

The total number of resuscitations by the method of stimulating the right auricle by a needle puncture is now about nine cases and includes the unpublished reports of Dr. Joseph B. Wolffe of Philadelphia and Dr. A. E. Parsonnet of Newark, both of whom have undertaken an investigation of this method in their respective cities.

A word in regard to the type of needle used may not be amiss; it has been found that a number 19 gage, all steel needle measuring at least $4\frac{1}{2}$ inches in length is best adapted for intracardiac injections of any

tractions may be as high as 300 beats per minute while the ventricular response may run as low as 80.⁴⁴

The sequential development of auricular extrasystoles, auricular flutter and auricular fibrillation is familiar to every cardiologist; such conditions are not incompatible with an active life on the part of the patient.⁴⁵ The prognosis of auricular disturbances of the heart is far more favorable than when such conditions affect the ventricles, the difference depending on the hemodynamic factors involved. Whereas irregularities of rhythm and output of the auricles may embarrass filling of the ventricular chambers, the same type of irregularities when occurring in the ventricles disarranges the entire circulation of the body, with immediate hazardous and sometimes fatal results.

A consideration of these facts would tend to indicate, therefore, that the dangers inherent from ventricular fibrillation following the intracardiac injection procedure for resuscitation of the stopped heart might be avoided, if not entirely eliminated, if the puncture was made in the auricles instead of in the ventricles.

A familiar laboratory experiment demonstrates that of the two, the auricles are far more sensitive to mechanical stimulation than the ventricles. In the resuscitation procedure, the auricles should thus be the portion of the heart best adapted physiologically for the reception of the injecting needle. The development of extrasystoles or even fibrillation of the auricles would be relatively unimportant for the reasons previously indicated.

Approach to the right auricle is not difficult. Experiments on cadavers showed that a slightly curved needle could be passed through the third interspace as close to the right sternal margin as possible and penetrate the right auricle. The needle must be directed toward the midline so that the curve carries the point under the sternum; after a little practice, the interns of the hospital found it no more difficult to penetrate the right auricle than to reach the left ventricle at the point generally recommended for intracardiac injection.

In children up to about the age of 12, the right auricle lies within 2 inches (5 cm.) of the anterior surface of the sternum, but in adults this depth may be greatly increased. Average figures obtained in a series of about forty cadavers showed that in thin persons this depth was about $3\frac{1}{2}$ inches (8.87 cm.), while in wide-chested persons the inserted needle must be at least $4\frac{1}{2}$ inches (11.43 cm.) long. In about 60 per cent of the cadavers examined, the injecting needle approached the right auricular appendage first. At this point there is little or no

44. Roth, I. R.: *Cardiac Arrhythmias*, New York, Paul B. Hoeber, Inc., 1928, p. 169.

45. Hyman, Albert S.: *Am. Med.* 22:469 (Aug.) 1927.

11. Intra-auricular puncture is no more difficult to perform than intraventricular injection; a slightly curved 4 inch needle is inserted into the third interspace at the right sternal margin. The point should be directed downward and toward the midline.

12. The auricles are more responsive to mechanical stimulation than the ventricles; a mere prick of the needle may be sufficient to initiate contraction.

13. Here, as in the ventricles, the first contractions are extrasystolic, the exception being that auricular extrasystoles are followed by normal ventricular contractions; hence the immediate establishment of the normal cardiovascular mechanism of circulation.

14. The sequential development of a rapid auricular extrasystolic arrhythmia, auricular flutter and finally fibrillation may not be of special significance so far as the ventricular output to the circulation is concerned, since the phenomenon of physiologic block slows the ventricular rate.

15. Intra-auricular puncture should be attempted in every case of death that occurs as the result of the asystolic heart. The cases most favorable for resuscitation are those not affected by general or cardiovascular disease. In deaths occurring on the operating table, after hemorrhage, shock, anesthesia or other ill defined conditions, like "status lymphaticus," prompt resuscitation may result from this procedure, either alone or combined with other life-saving measures—artificial respiration, transfusion, etc. In asphyxia neonatorum, it may be specific in its prompt initiation of automatic contraction of the heart.

16. Intra-auricular puncture is a procedure that every member of the medical profession should be able to perform quickly and skilfully when emergencies arise in which this life-saving operation may be indicated.

kind. Any gage finer than this becomes too flexible for penetration through the muscles of the chest, while gages larger than 19 become difficult to use. For the resuscitation procedure alone a hollow needle is unnecessary and a solid needle like a long hatpin can be utilized. A hollow needle has generally been used in our cases, since an associated study of intracardiac therapy for certain diseases of the heart has also been carried on by the committee investigating the resuscitation process.

CONCLUSIONS IN REGARD TO THE RESUSCITATION OF THE STOPPED HEART

1. The success of the intracardiac injection procedure for the resuscitation of the stopped heart is apparently due more to the effect of the puncture wound made in the wall of the heart than to the chemical substance injected.

2. The myocardium of the normal asystolic heart rapidly becomes irritable with the onset of anoxemia.

3. Under these conditions, any mechanical stimulation may irritate the heart to automatic contraction, and the success of massage and percussion of the heart for resuscitation can be explained on this basis.

4. The puncture wound made by the injecting needle becomes a focus of increased irritability from which a stimulus for myocardial contraction may be developed.

5. The first contractions of the heart after injection are always extrasystoles.

6. The initial extrasystolic arrhythmia may give way quickly to a normal sinus rhythm with prompt recovery on the part of the patient.

7. However, when the period of anoxemia has been so prolonged or so intense that there is considerable disturbance in the electrodynamic factors controlling myocardial contraction, the initial extrasystolic arrhythmia may persist and may be quickly followed by a rapid sequence of ectopic beats.

8. Such a condition leads to pathologic fatigue of the ventricles which may be followed by ventricular fibrillation.

9. Ventricular fibrillation is an extremely hazardous disturbance of the heart and is usually accompanied by immediate collapse of the circulation and death of the patient. This phenomenon explains the secondary collapse of the circulation often seen following what has apparently been a successful resuscitation of an asystolic heart.

10. It is suggested, therefore, that the intracardiac puncture be made into the right auricle instead of into the ventricles as is now practiced.

a considerable part of the apparent increase in the incidence and death rate of diabetes may be only an increase in the recognition of it. This is a statement that does not seem to be susceptible of definite proof.

My observations in China indicate that diabetes among the natives is of low incidence and mild character, and that it is accompanied by definite hypersensitivity to insulin.¹ Reed,² in 1915, pointed out the infrequency of the disease among the Chinese. This benign type of diabetes is prevalent among the Japanese, also. Iwai,³ in a study of hospital cases, saw little diabetic coma. He was particularly impressed by the great difference of the disease there as contrasted with that seen in western countries. Concepcion⁴ set forth a similar picture of the mildness of diabetes in the Philippines. It is also said to be infrequent and mild in India, except in the wealthy leisure class, especially that of the Hindus.⁵ Mitra⁶ called the disease the bane of Bengal, particularly of wealthy and indolent Bengales gentlemen. Christopherson⁷ said glycosuria is rare in the Egyptian Sudan. He saw only one case in five years. Martin⁸ remarked on the rarity of diabetes among the negroes of the west coast of Africa, but reported three cases as proof that it exists there. Palacios⁹ stated that the disease is mild in the coastal area of Venezuela, diabetic coma being practically unknown. The disease is infrequent and the production of acetone bodies slight.

In a symposium on diabetes in the tropics (at meetings of the British Medical Association in 1907),⁵ it seemed to be the consensus among physicians who had served in India and the East that in the poorer classes of natives diabetes was infrequent, but that in the wealthy classes and clerical or business classes it was prevalent. This prevalence is often attributed to the unusual nervous strain that these classes undergo in their constant contact with European civilization. The change of diet toward the European type, with more sugar and sweet wines, is often cited as a responsible factor. Cauthie¹⁰ said that Chinese who indulge in European food extensively are prone to have diabetes, while on their native diets they are very free from it. This observation was also made

1. Mills, C. A.: *China M. J.* **41**:914, 1927.

2. Reed, A. C.: *Am. J. M. Sc.* **151**:577, 1916.

3. Iwai, T.: *Arch. de méd. expér. et d'anat. path.* **27**:1, 1916.

4. Concepcion, I.: *J. Philippine Islands M. A.* **2**:57, 1922-1923.

5. Symposium on Diabetes in the Tropics, British Medical Association Meeting, Exeter, July 27 to Aug. 2, 1907, *Brit. M. J.* **2**:1051, 1907.

6. Mitra, A.: *Indian Lancet, Calcutta* **21**:897, 1903.

7. Christopherson, J. B.: *Brit. M. J.* **2**:1063, 1907.

8. Martin, M.: *Arch. f. Schiffs- u. Tropen-Hyg.* **10**:363, 1906.

9. Palacios, G. D.: *Chimie Pathologique Tropicale de la Région Atlantique, Caracas, Lit. y Tip. del Comercio.*

10. Cauthie, James: *Brit. M. J.* **2**:1063, 1907.

DIABETES MELLITUS

IS CLIMATE A RESPONSIBLE FACTOR IN THE ETIOLOGY? *

C. A. MILLS, M.D.

CINCINNATI

A stay of two years in North China so interested me in the possible relation of climate to the occurrence of certain metabolic diseases (diabetes, pernicious anemia, exophthalmic goiter and Addison's disease) that I decided to make a study of the distribution of these diseases in all countries where deaths from these causes are registered. The annual reports on vital statistics of the various countries supplied the data used. An effort has been made to work out the prevalence of each disease geographically by countries and, where possible, racially. The results are interesting and suggestive from the standpoint of etiology. In order that the bulk of data shall not exceed the limits of space, each disease will be dealt with separately, the subject of this communication being diabetes.

The most reliable statistics indicating the incidence of diseases are those on mortality, and with the "International List of the Causes of Death" in wide use, the rates in various countries may well be compared. The point of greatest variability is, of course, the ability of the physician in naming the cause of death. Undoubtedly, many cases of non-diabetic glycosuria are diagnosed as diabetes, while, on the other hand, numbers of patients have undiagnosed diabetes. Whether these errors counterbalance each other has not been ascertained. The diabetic death rate in cities with large diabetic clinics is not higher than in those without. In the United States the rate is lower in the rural than in the urban districts, while in England and Wales the opposite is the case. It would seem most likely, therefore, that the death rate represents a fairly true picture of the prevalence of the disease. This is all the more true in that all cases in which diabetes is named as a contributory cause of death are classified as cases of diabetes, no matter what the immediate cause of death may have been (except cases of pulmonary tuberculosis, diphtheria and typhoid fever).

It is true, however, that a certain proportion of the apparent increase in the diabetic death rate may be due to improved diagnostic methods. Many patients with mild diabetes discovered more or less by accident in the course of a laboratory examination have the diagnosis of diabetes attached to them for life, and after death, as well. In this way, perhaps

* Submitted for publication, Feb. 24, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

then the northern states from Michigan west, the middle states from the Atlantic ocean to the Pacific ocean and finally the northeastern states, with a rate 2.2 times as high as that of the southern group (table 1).

A grouping of the cities of over 100,000 population into three belts across the country from west to east shows equally striking differences in the diabetic death rate (table 2). Thus the rate rises from 14.1 per hundred thousand estimated population in the southern cities to 20.4 in the central area, and 23 in the north. And if one omits the four cities, Detroit, Toledo, Cleveland and Youngstown, from the northern group,

TABLE 1.—*Deaths from Diabetes Mellitus per Hundred Thousand Estimated Population in the States of the Registration Area of 1926**

Florida.....	11.8	California.....	18.6
South Carolina.....	7.6	Kansas.....	17.4
Alabama.....	7.6	Nebraska.....	19.3
Mississippi.....	8.1	Iowa.....	19.3
Louisiana.....	9.6	Missouri.....	15.3
Arizona.....	8.3	Illinois.....	19.8
Tennessee.....	7.6	Indiana.....	17.9
North Carolina.....	8.3	Ohio.....	18.0
Virginia.....	11.0	Pennsylvania.....	18.0
West Virginia.....	9.8	Delaware.....	16.4
Kentucky.....	9.3	Maryland.....	19.3
Mean for 11 states.....	9.9	New Jersey.....	20.3
Colorado.....	12.7	Mean for 12 states.....	18.3
Utah.....	12.1	Maine.....	22.5
Wyoming.....	9.9	Vermont.....	21.0
Montana.....	10.4	New Hampshire.....	23.4
Idaho.....	8.3	Massachusetts.....	20.2
Mean for 5 states.....	11.1	Connecticut.....	21.2
Washington.....	15.6	Rhode Island.....	21.8
Oregon.....	18.1	New York.....	24.4
North Dakota.....	15.6	Mean for 7 states.....	22.1
Minnesota.....	17.1		
Wisconsin.....	18.0		
Michigan.....	17.0		
Mean for 6 states.....	16.9		

* Figure given for each state is the mean of the rates for 1920, 1925 and 1926.

its rate rises to 24.3, which is more than 1.7 times the rate of the ten southern cities. The four cities named, with a mean rate of 15.9, fall so definitely out of line with other northern cities around them that an explanation was sought for in the statistics of population. The probable reason was readily found. During the last twenty years, these four cities, in particular, have shown a phenomenal increase in population, and a large percentage of this increase has come from the countries of southern Europe, including Russia. This inclusion of a large percentage of southern European nationalities serves as a likely cause of the low diabetes death rate in these cities, bringing it closer to that of the southern cities. Pittsburgh was affected to a slightly less degree. For instance, the percentage of foreign-born parents of children born in 1918 was 48 per cent for Cleveland, 44 per cent for Youngstown, 35 per cent for

by me in my contact with Chinese students. The ingestion of foreign food for some weeks seemed often to lead to boils and mild glycosuria, which readily disappeared under dietary adjustment. Cauthie likened the intolerance of the tropical or oriental natives for sugar to their well known lack of tolerance for alcohol. He also raised the question whether the prevalence of diabetes among the Jews might not be on some such basis. Morrison¹¹ found the death rate from diabetes in Boston to be highest in the Irish inhabitants, while table 6, given on a later page, shows the rate in Ireland to be low. Here, again, is a people showing a marked rise in diabetic death rate following their migration from a lower to a higher stage of industrialized civilization.

Gore¹² recently made a study of the world death rate from diabetes and concluded not only that the disease is infrequent in the tropics, but that it is showing the most alarming increase in rate in the United States, Canada, northern Europe, Australia and New Zealand. Williamson¹³ and Hoffman¹⁴ set forth similar data.

When one contrasts the diabetes in the Orient and Tropics, as described in the reports named, with the disease as it is known in the northern part of the United States, in Canada and north central Europe, one is led to wonder whether important factors other than race and diet may not be working to determine its etiology. It was in an effort to evaluate the climatic factor more closely that the present work was undertaken. Individual countries were studied by states or provinces, when possible; continents were studied as to the prevalence in the constituent countries, and finally the world distribution by countries was studied as completely as possible.

DIABETES IN VARIOUS COUNTRIES

United States.—Because of the climatic extremes to be found in the United States, both as to temperature and as to humidity, the study was begun with this country. The report of the Bureau of the Census "Mortality Statistics: 1926" in the registration area for 1920, 1925 and 1926 was used. In table 1 are given the rates for the states of the registration area. The rate given in each case represents the mean of the crude rates for 1920, 1925 and 1926, so that annual irregularities may be minimized. It is seen that the states may readily be arranged in geographic groups according to the diabetic death rate, the southern states being lowest, the western plateau and mountain states coming next.

11. Morrison, H.: Boston M. & S. J. **174**:54, 1916.

12. Gore, J. K.: A World's War on Diabetes, Newark, N. J., Prudential Insurance Company of America, 1927.

13. Williamson, R. T.: Med. Chron., Manchester **50**:234, 1909.

14. Hoffman, F. L.: Boston M. & S. J. **187**:135, 1922.

In any discussion as to why the South should have less diabetes than the North, one always encounters the question of the prevalence of the disease among the negroes. One usually hears the terms "uncommon" or "infrequent" with reference to the incidence of this disease among

TABLE 3.—*Diabetic Death Rate in Relation to Total Death Rate*

	Mean Crude Death Rate for 1920-1925-1926 per 1,000 Population	Mean Crude Diabetic Death Rate for 1920-1925-1926 per 100,000 Population	Diabetic Death Rate as Percentage of Total Death Rate
Southern States			
Florida....	13.8	11.8	0.85
South Carolina ..	13.0	7.6	0.58
Alabama.....	11.8 (1925-1926)	7.6	0.64
Mississippi.....	12.7	8.1	0.64
Louisiana ...	12.6	9.6	0.76
Arizona... ..	12.5 (1926)	8.3	0.66
Tennessee... ..	12.1	7.6	0.63
North Carolina ..	12.1	8.3	0.69
Virginia... ..	12.4	11.0	0.81
West Virginia	10.7 (1925-1926)	9.8	0.92
Kentucky..	11.7	9.3	0.80
Rocky Mountain States			
Colorado. . .	12.7	12.7	1.00
Utah.....	10.1	12.1	1.21
Wyoming.	8.2 (1925-1926)	9.9	1.21
Montana	9.0	10.4	1.13
Idaho... ..	7.0 (1925-1926)	8.3	1.19
Washington			
Oregon .	10.5	15.6	1.49
North Dakota	11.4	18.1	1.59
Minnesota.	8.4	15.6	1.93
Wisconsin	10.0	17.1	1.71
Michigan	10.7	18.0	1.68
	12.6	17.0	1.35
California			
Kansas .	13.6	18.6	1.37
Nebraska	10.7	17.4	1.63
Iowa.....	9.4	19.3	2.05
Missouri	10.2	19.3	1.90
Illinois...	12.2	15.3	1.25
Indiana .	12.0	19.8	1.65
	12.9	17.9	1.39
Ohio... .			
Pennsylvania	12.0	18.0	1.50
Delaware .	12.8	18.0	1.41
Maryland..	14.0	16.4	1.17
New Jersey	14.3	19.3	1.35
	12.3	20.3	1.65
Maine.....			
Vermont...	14.5	22.5	1.55
New Hampshire	14.9	21.0	1.41
Massachusetts ..	14.3	23.4	1.59
Connecticut	12.9	20.2	1.57
Rhode Island	12.1	21.2	1.75
New York...	13.0	21.8	1.68
	13.3	24.4	1.84
Registration states.	12.3	17.1	1.39

them, and the question arises whether this might not account for the low diabetic rate in the southern states. However, Lehman¹⁵ found that in the hospital it is as prevalent among negroes as among white people. In table 4 is given the mean of the rates for 1920, 1925 and 1926 for each

15. Lehman, I. I.: New Orleans M. & S. J. **63**:461, 1910-1911; Southern M. J. **14**:522, 1921.

Detroit and Pittsburgh and 21 per cent for Toledo. Only four other cities had 35 per cent, or more, of foreign-born parentage in that year, these being New York, Providence, Scranton and Buffalo. No reason can be found to explain why Buffalo should differ so markedly in its diabetic death rate from the other cities on Lake Erie.

Among the southern states, Florida ranks highest, just as does Colorado among the mountain and plateau states. One would be inclined to attribute this largely to migration from the north of wealthy

TABLE 2.—*Deaths from Diabetes Mellitus per Hundred Thousand Estimated Population in the Cities of the Registration Area of 1926 **

San Antonio.....	11.9	Spokane.....	20.8
Fort Worth.....	9.3	St. Paul.....	24.3
Dallas.....	14.2	Minneapolis.....	21.4
Memphis.....	16.0	Milwaukee.....	21.6
New Orleans.....	19.6	Chicago.....	22.5
Nashville.....	15.6	Grand Rapids.....	23.9
Atlanta.....	13.3	Detroit.....	15.0
Birmingham.....	13.1	Toledo.....	16.7
Richmond.....	16.6	Cleveland.....	16.8
Norfolk.....	11.9	Youngstown.....	15.1
Mean for 10 cities.....	14.1	Buffalo.....	26.0
San Francisco.....	21.7	Rochester, N. Y.	23.6
Oakland.....	21.2	Scranton.....	23.0
Salt Lake City.....	18.1	Albany.....	32.7
Denver.....	16.7	New York.....	25.7
Kansas City, Kan.	20.2	Newark.....	23.1
Kansas City, Mo.	15.6	Paterson.....	25.8
Omaha.....	22.0	Yonkers.....	26.4
Des Moines.....	17.4	Syracuse.....	27.7
St. Louis.....	20.1	Jersey City.....	20.0
Indianapolis.....	21.1	New Haven.....	29.4
Louisville.....	19.5	Springfield, Mass.	22.7
Cincinnati.....	26.8	Providence.....	24.7
Dayton.....	22.0	Fall River.....	20.8
Columbus.....	21.3	Boston.....	23.6
Pittsburgh.....	19.1	Mean for 25 cities.....	23.0
Philadelphia.....	21.2	Mean for Detroit, Toledo, Cleve-	
Baltimore.....	24.2	land and Youngstown.....	15.9
Washington.....	19.7	Mean for 21 other cities.....	24.3
Wilmington.....	18.0	Two cities showing greatest in-	
Mean for 19 cities.....	20.4	crease in 1926 were Albany (102%)	
		and Spokane (93%)	

* Figure given for each city is the mean of the rates for 1920, 1925 and 1926.

people, among whom diabetes is more common. The same discrepancy is seen in the death rate from pernicious anemia in these two states (as will be shown in a subsequent paper).

Thinking that perhaps a low total death rate in the western states might account for the low diabetic rate, I prepared a table showing the percentage of the total deaths that were classified as resulting from diabetes. Table 3 presents this data for the forty-one states of the registration area, the mean of the rates for 1920, 1925 and 1926 being used, except as indicated. When viewed in this light, the southern states stand alone, with percentages well below 1 per cent, the mountain and plateau states coming next with figures slightly above 1 per cent, while the percentages of the rest of the northern states range up to more than 2 per cent.

In order to be sure that age and sex differences in the population of the various states are not the factor responsible for the differences seen in the incidence of diabetes, the states were arranged in the same groups as before, and the adjusted diabetic death rate was studied for the year 1921.¹⁶ The mean rate for the southern states rose from 9.2 to 9.8, that for the western mountain states from 12.8 to 14.3, while the rate for the northern states fell, the fall being greatest in the New England states that had the highest rate. The rate here fell from 23.6 to 19.7. Thus, although the use of adjusted rates tends to lessen the divergence north and south, the same geographic differences are maintained, the mean southern rate being less than half the northeastern rate.

A similar comparison of the crude and the adjusted diabetic rates for 1921 in the eleven states in which the classification is by color shows the adjusted rate for white people to be 12.6 and the crude rate 12.4, while

TABLE 5.—*Death Rate from Diabetes in Canada*

	Total Number of Deaths per 1,000 Population	Deaths from Diabetes per 100,000 Population	Deaths from Diabetes as Percentage of Total Number of Deaths
Prince Edward Island.....	12.0	10.6	0.88
Nova Scotia.....	12.2	11.1	0.91
New Brunswick.....	12.8	11.1	0.87
Quebec.....	14.5 (1926)	11.0	0.76
Ontario.....	11.35	11.9	1.05
Manitoba.....	8.55	8.2	0.96
Saskatchewan.....	7.45	6.2	0.83
Alberta.....	8.35	8.0	0.96
British Columbia.....	8.95	11.0	1.23

* Mean rates for the years from 1921 to 1926, inclusive.

the adjusted rate for colored people is 9.9 as compared with a crude rate of 8.4. The adjusted rate for the colored race shows the same marked increase as one goes northward as was seen in table 4. New York and Pennsylvania, not given in table 4, have an adjusted rate for the colored population much higher than that in the south. In Pennsylvania, the rate is 5 higher than that for the white race.

Canada.—The diabetic death rate of Canada as a whole is considerably below that of the United States, but shows the same variations from east to west as does the northern half of the latter country. Table 5 shows the mean crude rate per hundred thousand of population for the years 1921 and 1926 in the various provinces and the deaths from diabetes as percentages of the total number of deaths.

One sees here that the greatest incidence of diabetes in Canada is in those provinces nearest to the New England states, where the death rate from diabetes in the United States is highest. Also, the prairie provinces

16. Gover, Mary: Pub. Health Bull., no. 174, U. S. P. H. S., Washington, 1928.

of the states in which deaths are classified by race. The term "colored" includes all races other than the white, but refers so preponderantly to the negro that other races in the South can be disregarded. In table 4, it is seen that there are almost as many deaths from diabetes among the "colored" as among the "white" population, in two states the number of deaths among the "colored" even being the greater. It is also important to notice that the three states having the highest diabetic death rate among colored persons are the states located farthest north in the group given. A geographic grouping of the cities, in which classification is by race, again

TABLE 4.—Deaths from Diabetes Mellitus per Hundred Thousand Estimated Population in the States and Cities of the Registration Area in Which Classification into "White" and "Colored" Is Made

States	Death Rate per 100,000		Cities	Death Rate per 100,000	
	White	Colored		White	Colored
Alabama.....	7.8	7.0	Fort Worth.....	9.5	7.9
South Carolina.....	9.2	6.1	Dallas.....	14.2	15.3
North Carolina.....	8.7	7.4	Birmingham.....	15.2	9.8
Tennessee.....	7.4	8.4	Atlanta.....	13.1	14.2
Mississippi.....	10.1	6.3	New Orleans.....	19.5	19.9
Louisiana.....	10.7	7.8	Memphis.....	16.5	15.3
Florida.....	14.3	6.6	Nashville.....	15.3	16.0
Kentucky.....	9.0	12.4	Norfolk.....	13.0	9.5
Virginia.....	11.3	10.2	Richmond.....	18.2	12.8
Maryland.....	20.6	13.1			
Mean rate.....	9.8	8.5	Mean rate.....	14.9	13.4
			Washington.....	18.7	22.9
			Baltimore.....	25.4	17.3
			Louisville.....	20.0	16.8
			Indianapolis.....	21.8	15.6
			Kansas City, Mo.	19.9	22.3
			Mean rate.....	21.2	19.0
			Mean rate for all the above cities.....	17.1	15.4

emphasizes the points just mentioned: that diabetes is almost as prevalent in the negro as in the white race, and that the rate increases with about equal rapidity in both races as one goes from south to north. In two states and six large cities, the rate for the colored is higher than that for the white population.

In view of these observations, it may well be concluded that the negro is not responsible for the low diabetic death rate in the southern states. The statistics for the negro race greatly strengthen the evidence pointing toward a climatic effect in the etiology of diabetes. In two districts of Nigeria, where registration of death by cause is compulsory, the diabetic death rate among the natives in 1926 and 1927 was less than one per hundred thousand of population. The farther the negro gets from his natural tropical environment, the higher the number of deaths from diabetes. It would be extremely interesting to have a similar study of the Jews to see whether the high incidence of diabetes among them lessens with a lessening of the distance from the equator.

were: Nigeria, 1; southern Rhodesia (European population), 8, and Union of South Africa, 11.6. Even this limited number arrange themselves with an increasing rate as the distance from the equator increases.

In Asia, the rate for a whole population was given only in three countries: Japan, 3.19; Straits Settlement, 2.7, and Ceylon, 6.5. A few city rates are given, and many for hospitalized population, but these are of little value in such a study as this.

It is of particular interest to note that Japan, lying as far north as it does, has a tropical rate. The same is true of the whole of China, although no reliable statistics are available. What relation this low rate bears to the severe tropical summer that prevails along the entire coast of Asia is questionable. The coincidence, however, is suggestive.

On the basis of latitude, one would expect China to show the same difference in incidence of diabetes north and south as is encountered in

TABLE 7.—*Mean Diabetic Death Rate per Hundred Thousand Population in Australia, Tasmania, and New Zealand for the Years from 1921 to 1927 Inclusive*

1. Western Australia	10.2
2. Northern Territory.	0.0
3. Queensland.....	9.3
4. South Australia..	15.3
5. New South Wales.	11.7
6. Victoria.....	12.1
7. Tasmania.....	13.5
8. New Zealand	11.9

the United States. The winters in North China are severe, as contrasted with those in South China, but the summers are about equally depressing throughout. In South America, the rate is everywhere low. Time relationships in the data of these countries are not sufficiently uniform to warrant a close comparison.

Throughout the Registration Areas of the World.—In table 8 are presented the death rates from diabetes by countries for all areas giving such data. It is seen here that certain areas of the earth supply all the high rates, these being northwestern Europe (including the British Isles), the United States and Canada in North America, southern Africa, and Australia, Tasmania and New Zealand. These countries are the ones principally dominated by the people from northern Europe, but one cannot safely assume that this accounts for the high incidence of diabetes. For instance, Anglo-Saxons of the United States have a high rate in the North and a low one in the South. Rather, it seems better to assume that the same advantageous factors that led to the development in these regions by northern Europeans, may also be causing the increase in diabetes. The climatic stimulation, in increasing the vigor and ambition of the people so as to lead to great developments along all lines of

have a low rate corresponding to that of the western plateau and mountain states in this country. The same elevation is again noted for the Pacific coast. However, when one considers only the proportion of the total number of deaths due to this cause, there are no striking differences in the different provinces.

The Registration Countries of Europe.—The death rate from diabetes was available for fourteen countries of Europe, as given in table 6. When one groups the countries into those with a rate above 9.6 and those with one of 9.6 or below, as is done in table 6, a striking geographic separation is seen. With the exception of Ireland, all the countries above the fiftieth parallel the death rate of which is available, have a death rate from diabetes above 9.6, while all below that parallel have a rate of 9.6 or below. Thus, with the exception of Ireland, the fiftieth

TABLE 6.—*Diabetic Death Rate in the Countries of Europe*

Countries	Year	Diabetic Death Rate per 100,000 of Population	Deaths from Diabetes as Percentage of Total Number of Deaths
Netherlands.....	1927	16.3	1.59
Denmark.....	1927	12.9	1.12
England and Wales.....	1927	12.6	1.02
Belgium.....	1927	13.3	0.99
Sweden.....	1925	11.3	0.96
Norway.....	1926	9.7	0.90
Scotland.....	1927	10.6	0.79
North Ireland.....	1927	9.6	0.66
Switzerland.....	1925	9.2	0.75
Spain.....	1926	8.5	0.45
Irish Free State.....	1927	7.8	0.53
Italy.....	1925	5.9	0.35
Czechoslovakia.....	1926	5.4	0.36
Hungary.....	1927	4.3	0.24

parallel forms a sharp division in the incidence of diabetes in Europe. This difference north and south is even more striking when one considers the deaths from diabetes in relation to the total deaths, as is done in the second column of table 6. A further point of great importance is that the rate is at present increasing much more rapidly in the northern European countries than in the southern. No doubt Germany would fall in the northern group if the country's rate were available. Morrison ¹¹ found that the German inhabitants in Boston had a comparatively high rate.

Australia, Tasmania and New Zealand.—In Australia, Tasmania and New Zealand, one has, again, a large area showing a distribution of diabetes north and south, just the reverse of that of Europe and the United States. Table 7 shows this increase toward the south and away from the equator.

Africa, Asia and South America.—The only data available for Africa on deaths from diabetes per hundred thousand of population

the more intense type of living necessary in the highly industrialized areas causes the increase or the same climatic factors that cause the development of the area likewise increase the disease. There is a strong correlation between Huntington's "energy maps" of the world¹⁷ and the rate maps for diabetes which one may construct from the data given here. Where he found the climatic stimulation most evident in the energy of the people, there also one finds the highest incidence of diabetes. This holds for the different parts of the United States, as well as for the whole world. It fails to hold, however, for Japan.

COMMENT AND SUMMARY

The significance of the salient points in the data has been discussed as the figures were presented in each section. It may be well, however, to emphasize still further certain features of the presentation.

That the incidence of diabetes in the southern states is definitely and markedly lower than in the northern states of this country is beyond doubt. This difference is about equally great for both white and colored races as one goes from south to north. Nor can the low southern rate be attributed to the large negro population, for the death rate of the latter from diabetes is only slightly below that of the white population in any given state. In fact, in a few states and cities it is higher.

This same climatic distribution of the disease is seen also in Australia, Tasmania and New Zealand, where the rate increases as the distance from the equator becomes greater. This occurs with practically a homogeneous population. In Europe, one finds a division along the fiftieth parallel, with a high rate north and a low rate south. That this division should be found in Europe, with its great diversity of people, and with no outstanding dietary factors to which it might be attributed, forms a rather strong indication of climatic effect.

Japan and north China, with the scarcity and mildness of the diabetes of these countries, supply an apparent exception to the climatic distribution, but here one may readily attribute the low rate to the long moist tropical summer which along the Asiatic coast extends almost to the Arctic circle.

Many writers have suggested that increased consumption of sugar may be the major factor responsible for the increase in diabetes. It seems undoubtedly true that certain races do exhibit a proneness to diabetes when they leave their native diets for the foreign foods containing more sugar (Chinese, especially). It may also be true that the people of the northern section of the United States consume more sugar

17. Huntington, Ellsworth: *World Power and Evolution*, New Haven, Conn., Yale University Press, 1920, p. 230.

endeavor, may also be causing the body to exceed its metabolic capacity in various ways. This overwork, or exhaustion, may show itself in diabetes mellitus, suprarenal insufficiency of the degree seen in the so-called "neurocirculatory asthenia" and particularly in nervous and mental diseases of the exhaustive type. Unfortunately, accurate statistics

TABLE 8.—*Death Rate from Diabetes Mellitus in the Registration Countries of the World*

Country	Year	Crude Diabetic Death Rate per 100,000 of Population	Deaths from Diabetes as Percentage of Total Number of Deaths
United States.....	1926	18.0	1.47
Netherlands.....	1927	16.3	1.59
New Zealand.....	1927	13.7	1.62
Belgium.....	1927	13.3	0.99
Denmark.....	1927	12.9	1.12
Australia.....	1927	12.9	1.37
England and Wales.....	1927	12.6	1.02
South Africa.....	1926	11.8	1.23
Canada.....	1927	11.4	1.14
Sweden.....	1925	11.3	0.96
Scotland.....	1927	10.6	0.79
Norway.....	1926	9.7	0.90
North Ireland.....	1927	9.6	0.66
Switzerland.....	1925	9.2	0.75
Spain.....	1926	8.5	0.45
Hawaii.....	1927	8.5	0.75
Southern Rhodesia (Europeans only)...	1925	8.0
Saar Basin.....	1927	8.0
Irish Free State.....	1927	7.8	0.53
Barbados.....	1927	7.1	0.35
Province of Buenos Aires.....	1924	6.7	0.60
Ceylon.....	1928	6.4	0.26
Italy.....	1925	5.9	0.35
Uruguay.....	1927	5.5	0.48
Czechoslovakia.....	1926	5.4	0.36
Curacao.....	1927	4.7
Hungary.....	1927	4.3	0.24
Jamaica.....	1927	4.2	0.19
Grenada.....	1927	4.1	0.26
Cuba.....	1925	4.1	0.32
Paraguay.....	1928	3.7	0.25
British Guiana.....	1928	3.7	0.13
Colombia.....	1927	3.5	0.24
Argentina.....	1913	3.5	0.22
Chile.....	1927	3.5	0.14
Japan.....	1924	3.2	0.15
Costa Rica.....	1927	3.1	0.21
Straits Settlement.....	1927	2.8	0.09
Venezuela.....	1918	2.5	0.13
Iceland.....	1911-1915	2.0	0.14
Province of Mendoza.....	1924	2.0	0.11
Province of Tucumán (Argentina)....	1928	1.5	0.08
Panama.....	1926	1.1	0.09
Nigeria.....	1926	1.0	0.04
Philippine Islands.....	1925	0.5	0.03
Haiti.....	1927	0.4	0.08

can be had only for diabetes. In a subsequent paper, it will be shown that pernicious anemia has a distribution similar to that of diabetes, indicating the possibility of its also having a climatic relationship.

A strong argument against the claim that the racial factor is the most important in the distribution of diabetes is the marked change in the death rate from diabetes of the negroes in this country as one goes from south to north, a change even more marked than that of the corresponding rate for the white race. It would seem much more likely that either

DIABETES MELLITUS

SUGAR CONSUMPTION IN ITS ETIOLOGY *

C. A. MILLS, M.D.

CINCINNATI

In the preceding paper on the relation of climate to the death rate from diabetes,¹ a definite climatic distribution of the disease was pointed out. In the United States, for instance, the death rate from diabetes was over twice as high in the northern as in the southern states, and this difference was even more marked in the colored than in the white population. Europe showed a similar increase in the death rate from diabetes toward the north, as did the provinces of Australia and New Zealand in the opposite direction. This definite tendency in the distribution of the disease raises the question of whether climate is the responsible factor, or whether a higher rate of consumption of sugar in the northern states and countries might not cause the increase. It has often been suggested that overindulgence in sugar may bring on diabetes, a suggestion that seems to be borne out frequently by case histories. However, no definite proof has yet been offered. Emerson and Larimore² were of the opinion that a rather close relationship existed between annual consumption of sugar and the death rate from diabetes in the United States, Great Britain and Paris. If a cause and effect relationship were to exist, one would expect a lag of several years in the rise of diabetes rather than a parallelism with the consumption of sugar, since only the initiation of the disease would thus be influenced and not its course or duration under treatment.

In the accompanying table is given the consumption of sugar in kilograms per capita for five years (1923-1928), together with the death rate from diabetes for the most recent year obtainable, and the deaths expressed from diabetes as a percentage of the total deaths. A study of this table fails to show any direct relationship between consumption of sugar and deaths from diabetes. Some countries with a high consumption of sugar, as Hawaii, Argentina and Cuba, have a relatively low death rate from diabetes, while some of the countries with a high death rate from diabetes, such as the Netherlands and the Union of

* Submitted for publication, March 3, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

1. Mills, C. A.: Diabetes Mellitus: Is Climate an Important Etiologic Factor? Arch. Int. Med., this issue (46:569, 1930).

2. Emerson, Haven; and Larimore, Louise S.: Diabetes Mellitus, Arch. Int. Med. 34:585 (Nov.) 1924.

than do those in the south, although no proof either for or against this is at hand. But in Europe one can scarcely accept dietary differences as responsible factors in determining the incidence of diabetes north and south. Nor would there exist such a difference in diagnostic ability in the medical profession in northern and southern Europe.

Racial traits have also been credited with determining the incidence. But here one can cite the low rate for the Irish in Ireland and the high rate for this nationality in this country (Boston), also the difference in the Chinese when they live on their native diets and when they eat foreign foods. The negroes, again, contradict the assumption of a racial element, with their extremely low rate in Africa, moderately low rate in the southern states and high rate in the northern states of this country.

One can therefore scarcely avoid the conclusion that climate is a factor that is, in part at least, responsible for the incidence of diabetes in all races. The regions possessing the most changeable and stimulating climate are the ones with the highest incidence of diabetes. In some of these, it is true, life is intense and complex, and the sugar consumption high, indeed, but in certain others, equally stimulating, almost the same frequency of diabetes is seen without the high sugar consumption to which to attribute it. One is inclined to attribute the increase in diabetes and consumption of sugar to the same cause, namely, overstimulation by a highly changeable climate, leading to a desire for the sugars as readily available producers of energy, but also leading to an increase in diabetes whether this desire for sweets is satisfied or not. The increase is probably much more marked where the prosperity of the people permits them to indulge this desire without stint. Prosperity may also act by lessening the physical effort required, thus making the intake of sugar still more excessive so far as physiologic needs are concerned.

South Africa, come fairly well down in the column of sugar consumption. It is to be noted, however, that of the thirteen countries highest in consumption of sugar, eleven are found among the thirteen highest in death rate from diabetes (including England and Wales, Scotland and North Ireland under the heading of Great Britain).

In like manner, when one considers particular countries, there is again found no constant relationship between the consumption of sugar and the death rate from diabetes. In some that have shown a gradual but steady increase in the consumption of sugar for many years, there has occurred a recent decline in deaths from diabetes. Norway is an instance of this fact, with a consumption of sugar rising gradually from 4.5 Kg. per capita in 1866-1870 to 30.4 Kg. in 1927 and to 31.4 in 1928, while the death rate from diabetes has declined from 11.9 in 1922 to 9.7 in 1926. In Australia, with a high consumption of sugar, the number of deaths from diabetes showed little or no tendency to increase from 1921 to 1926. New Zealand, with a rather marked decline in the consumption of sugar (46.0 Kg. in 1923, 50.0 in 1924, 37.7 in 1925, 34.1 in 1926, and 29.5 in 1927) continues with practically no change in the death rate from diabetes. Hawaii, with a high consumption of sugar for several years, is exhibiting a considerable increase in diabetes. In the United States, the consumption of sugar has been fairly constant for several years, but diabetes continues its alarming increase.

I might cite various other instances to illustrate the lack of any uniformity between the intake of sugar and the deaths from diabetes, but the variability is so great that no further details seem necessary. Lack of space prevents the presentation of all the data on which these statements are made, but the study of the entire mass of data leaves little doubt in my mind that consumption of sugar as such is not related in a causal way to the death rate from diabetes.

Table Showing Consumption of Sugar and Death Rate from Diabetes

Country	Consumption of Sugar, Kilograms per Capita					Country	Year	Crude Estimate of Death Rate from Diabetes per 100,000 of Total Population	Deaths as Diabetes Percentage of Total Deaths
	1923-1924	1924-1925	1925-1926	1926-1927	1927-1928				
Australia.....	59.0	58.7	58.3	58.2	58.0	New Zealand.....	1927	13.7	1.62
Hawaii.....	54.4	54.7	55.0	55.0	55.1	Netherlands.....	1927	16.3	1.59
Denmark.....	48.2	49.7	53.8	48.6	51.7	United States.....	1926	18.0	1.47
United States.....	49.2	52.5	52.2	51.3	49.6	Australia.....	1927	12.9	1.37
Argentina.....	27.8	30.0	32.7	31.9	31.1	South Africa.....	1926	11.8	1.23
Cuba.....	33.1	35.6	46.6*	44.9	44.3	Canada.....	1927	11.4	1.14
Great Britain.....	38.4	40.6	41.2	41.1	44.8	Denmark.....	1927	12.9	1.12
Switzerland.....	36.8	36.3	39.7	34.3	42.5	England and Wales.....	1927	12.6	1.02
Canada.....	40.0	41.9	41.4	40.3	40.8	Belgium.....	1927	13.3	0.99
Sweden.....	33.8	37.1	37.0	35.9	37.7	Sweden.....	1925	11.3	0.96
New Zealand.....	40.0	50.0	37.7	34.1	29.5	Norway.....	1926	9.7	0.90
Norway.....	23.0	28.0	27.0	30.4	31.4	Scotland.....	1927	10.6	0.79
Netherlands.....	26.8	28.6	28.7	26.3	30.0	Switzerland.....	1925	9.2	0.75
Austria.....	22.9	26.7	20.8	26.3	30.0	Hawaii.....	1927	8.5	0.75
Czechoslovakia.....	25.8	27.6	23.6	25.7	27.0	North Ireland.....	1927	9.6	0.60
Belgium.....	21.9	24.9	24.6	24.4	26.4	Province of Buenos Aires.....	1924	6.7	0.60
Germany.....	14.6	22.2	22.6	23.9	25.4	Irish Free State.....	1927	7.8	0.53
France.....	20.6	23.1	24.2	20.1	23.8	Uruguay.....	1927	5.5	0.48
British Guiana.....	21.4*	Spain.....	1926	8.5	0.45
South Africa.....	17.0	17.5	19.1	20.0	20.3	Czechoslovakia.....	1926	5.4	0.36
Uruguay.....	22.3*	21.4*	Barbados.....	1927	7.1	0.33
Chile.....	25.0*	20.2*	Italy.....	1925	5.9	0.35
Central America.....	13.1	12.4	12.4	14.5	14.5	Cuba.....	1925	4.1	0.32
Hungary.....	6.0	10.2	11.0	12.4	13.5	Grenada.....	1927	4.1	0.25
Mexico.....	10.1	10.6	11.6	13.3	13.3	Paraguay.....	1928	3.7	0.25
Poland.....	7.2	9.8	10.1	11.5	12.7	Hungary.....	1927	4.3	0.24
Japan and Formosa.....	8.4	8.6	9.3	9.2	10.3	Colombia.....	1927	3.5	0.24
Japan.....	12.4*	12.7*	Argentina.....	1913	3.5	0.22
Portugal.....	12.7*	12.7*	Costa Rica.....	1927	3.1	0.21
Spain.....	10.5	10.8	10.8	11.9	12.2	Jamaica.....	1927	4.1	0.19
Jamaica.....	11.5*	Japan.....	1924	3.2	0.15
Philippine Islands.....	9.5*	Chile.....	1927	3.5	0.14
Italy.....	8.7	8.4	8.9	8.9	9.1	British Guiana.....	1928	3.7	0.13
Russia.....	3.2	5.3	7.1	7.4	8.9	Province of Mendoza (Argentina).....	1924	2.0	0.11
Haiti and Santo Domingo.....	3.8	3.9	3.8	4.3	4.2	Province of Tucuman.....	1928	1.5	0.09
China.....	2.1	2.4	2.3	2.0	2.2	Panama.....	1926	1.1	0.08
						Haiti.....	1927	0.4	0.08
						Philippine Islands.....	1925	0.5	0.05

* The figures for consumption of sugar were taken mainly from a bulletin on sugar issued by the League of Nations ("The World Sugar Situation," Report by the Economics Committee of the League of Nations, Geneva, July 4, 1929.) They were checked, in most instances, against consumption as obtained from the annual statistical reports of the various countries. When considerable discrepancy was found or when no data were given in the bulletin, the figures obtained directly from the original annual reports are given.

If a correct count of the platelets in the circulating blood is to be obtained and a satisfactory normal standard reached, all these facts must be taken into consideration.

The essentials of a good method for counting blood platelets are:

1. A satisfactory preserving fluid.
2. Absence of contact between the undiluted blood and any surface to which the platelets tend to adhere.
3. A technic for the enumeration of the platelets which obviates the necessity of the graduated pipet and of the counting chamber.

THE PRESERVING FLUID

The lack of a satisfactory preserving fluid is the source of error in many of the methods. It is not easy to find a fluid in which the platelets do not stick to one another, to the erythrocytes or to the

TABLE 1.—*Average Number of Blood Platelets per Cubic Millimeter of Normal Blood as Determined by Various Methods*

Average Number of Platelets per C.Mm.	Author
150,000-200,000	Sahli, H.: <i>Ztschr. f. klin. Med.</i> 56 : 264, 1905
225,000	Helber, E.: <i>Deutsches Arch. f. klin. Med.</i> 81 : 316 (Sept.) 1904
234,000	Fonio, A.: <i>Deutsche Ztschr. f. Chir.</i> 117 : 176 (June) 1912
260,000	Bizzozero, J.: <i>Virehows Arch. f. path. Anat.</i> 90 : 261, 1882
297,000	Wright, J. H., and Kinnicutt, R.: <i>J. A. M. A.</i> 56 : 1457 (May 20) 1911
300,000	Kristenson, A.: <i>Acta med. Scandinav.</i> 57 : 301, 1922
366,000	Gram, H. C.: <i>Acta med. Scandinav.</i> 54 : 1, 1920-1921.
469,000	Pratt, J. H.: <i>J. A. M. A.</i> 45 : 1999 (Dec. 30) 1905
500,000	Prus, J.: <i>Medycyna</i> , 1886, nos. 39 and 40; abstr., <i>Centralbl. f. klin. Med.</i> 8 : 469 (June 18) 1887
600,000	Puchberger, G.: <i>Wien. med. Wehnschr.</i> 55 : 1402, 1905
635,000	Brodie, T. G., and Russell, A. E.: <i>J. Physiol.</i> 21 : 330 (May 12) 1897
635,000	Zeller, H.: <i>Ztschr. f. d. ges. exper. Med.</i> 10 : 103, 1919-1920
760,000	Flössner, O.: <i>Ztschr. f. Biol.</i> 77 : 113, 1922-1923
778,000	Kemp, G. T., and Calhoun, H.: <i>Brit. M. J.</i> 2 : 1539 (Nov. 23) 1901
862,000	Kemp, G. T., and Calhoun, H.: <i>Am. J. Physiol.</i> 5 : 4, 1901

leukocytes or to the apparatus employed, particularly glassware. Numerous solutions have been proposed and used as preserving fluids. Solutions of many neutral salts, i. e., indifferent fluids, as of sodium chloride, magnesium sulphate, etc., have been employed. Various fixing reagents have been recommended, such as Hayem's fluid and Ferrier's fluid (consisting of alcohol, glycerin, fuchsin and water). Solutions of anticoagulants have been used a great deal, for example, solutions of citrates, oxalates, etc. Besides these, a great many solutions of organic substances, both of synthetic and of natural origin, have been advocated. Hypotonic, isotonic and hypertonic, hemolytic and non-hemolytic solutions have been tried and accepted or rejected by various investigators.

The preserving fluid, to be satisfactory, must first of all rapidly fix and preserve both the blood platelets and the erythrocytes. If not quickly fixed and preserved, the former tend to disintegrate promptly into coarse refractile granules, while the latter are apt to undergo

BLOOD PLATELETS

AN IMPROVED INDIRECT METHOD FOR THEIR ENUMERATION *

ISADORE OLEF, M.D.

BOSTON

Numerous methods for counting blood platelets have appeared since Schultze's ¹ original description in 1865 of these "granular formations" as microscopic cellular constituents of normal blood. Hittmair ² in his recent review of the literature referred to twenty new methods that had appeared within the previous ten years. That these methods are for the most part unsatisfactory is indicated by the wide range of supposedly normal figures reported, as shown in table 1.

These wide differences may be explained by improper technic, which involves two kinds of errors: (1) loss or destruction of blood platelets and (2) the inclusion in preparations of artefacts and foreign matter which are mistaken for platelets. The first results in counts too low, the second in counts too high. The difficulties encountered by various investigators are undoubtedly due to the peculiar physical characteristics of the platelets; viz., their great tendency to agglutination, adhesion and easy disintegration, which may occur as soon as they come under conditions that differ from those existing within normal blood vessels. To these must be added their small size and light weight.

Boshamer ³ in his recent investigations found that the blood platelets may be classified into four types: (1) small or young forms, about one-fourth the diameter of a red cell; (2) round to rod-shaped forms, from about one-fourth to two-thirds the diameter of a red cell; (3) rod-shaped forms, and (4) large or giant forms, over two-thirds the diameter of a red cell. Type 1, according to Boshamer, is the most abundant, but also the least resistant, and under unfavorable conditions is apt to undergo rapid disintegration, reducing at times the normal platelet count to one-half its true value.

* Submitted for publication, Feb. 18, 1930.

* From the Medical Clinic of the Boston Dispensary, Service of Dr. Joseph H. Pratt, and the Division of Research.

1. Schultze, M.: Ein heizbarer Objecttisch und seine Verwendung bei Untersuchungen des Blutes, *Arch. f. mikr. Anat.* **1:1**, 1865.

2. Hittmair, A.: Die Blutplättchen (review of the literature for ten years), *Folia haemat.* **35:156**, 1928.

3. Boshamer, K.: Ueber Zählung, Resistanz, und Neubildung von Blutplättchen, *Ztschr. f. d. ges. exper. Med.* **48:631**, 1925-1926.

are never clumped, but are discrete and freely movable. No precipitate is formed to obscure the field or to be confused with the platelets. The specific gravity is relatively low, allowing rapid sedimentation of the platelets. It is inexpensive and easily prepared.

In the course of this investigation, it was thought desirable to make comparative studies by the technic to be described, with the following preserving fluids:

1. Kemp and Calhoun's solution,⁸ composed of 1 part of 40 per cent formaldehyde solution and 15 parts of 1 per cent sodium chloride solution, tinged with either methyl green or methyl violet; the fluid is therefore approximately 2.5 per cent formaldehyde and 1 per cent sodium chloride. This solution acts as a good preservative, but only for a relatively short time; at the end of from fifteen to twenty minutes, numerous "Arnold bodies" appear in the preparations, either free or in the process of separation from the red cells. Employing the indirect method, Kemp and Calhoun determined the number of erythrocytes with the hematocrit, and the ratio of platelets to erythrocytes in a Thoma-Zeiss counting chamber. This method involves considerable error, owing to the employment of the counting chamber, for it permits the inclusion in the platelet count of "Arnold bodies," which are not readily differentiated from platelets when the high dry lens is used. In fact, Kemp⁹ claimed that he saw platelets which contained hemoglobin and at times were attached to the red cells, these platelets being identical with Hayem's "globules nains." The latter investigator¹⁰ believed that these small formations were hemoblasts, i. e., precursors of erythrocytes. In discussing Kemp's paper, which was presented before the Johns Hopkins Hospital Medical Society, Osler remarked: "I have spent many weary hours over them [referring to platelets], but I never caught one blushing." These blushing platelets were undoubtedly "Arnold bodies" which were mistaken for platelets. The average number of platelets per cubic millimeter, as indicated by a mean of seventy-five observations on nineteen different persons, was found by Kemp and Calhoun to be 778,000. In another series¹¹ of determinations, the average number of platelets per cubic millimeter based on fourteen different counts from eleven men and six different counts from two women was 862,000 for men and 833,000 for women. In still another

8. Kemp, G. T., and Calhoun, H.: Enumeration of Blood Platelets: Their Relation and that of the Leucocytes to Blood Coagulation, *Brit. M. J.* **2**:1539 (Nov. 23) 1901.

9. Kemp, G. T.: The Effect of Altitude on Blood Plates and Blood Corpuscles, *Bull. Johns Hopkins Hosp.* **15**:177 (May) 1904.

10. Hayem, G.: *Du sang*, Paris, 1889.

11. Kemp, G. T., and Calhoun, H.: Some New Observations on Blood Plates and Leucocytes, *Am. J. Physiol.* **5**:4, 1901.

degenerative changes with the production of artefacts, usually in the form of "Arnold bodies." It must also prevent the sticking together of the platelets, for they must remain freely movable in the preparation in order to be easily identified when examined in clear solution. Furthermore, the preserving fluid must have a relatively low specific gravity, which will allow fairly rapid sedimentation of the platelets. Isotonicity of the preserving fluid is important, for when the diluting fluid is hypotonic or hypertonic artefacts are formed, usually from the erythrocytes, which may be mistaken for platelets, particularly when the ordinary counting chamber and high dry lens are used. When a direct or an indirect platelet count is made, bacteria, if present in the diluting fluid, often simulate platelets; it is therefore important to work with fairly stable solutions that do not become readily contaminated. A number of solutions proposed contain a dye that stains the platelets. These usually have the disadvantage of containing a fine precipitate which at times interferes with the platelet count.

With the oil immersion lens I examined, after filtering them, the solutions of Rees and Ecker,⁴ Buckman and Hallisey⁵ and Wright and Kinnicutt,⁶ and found that each contained a fine precipitate that either obscured the field or was easily confused with platelets.

In this investigation, a 2 per cent solution of sodium metaphosphate was employed, as originally recommended by Pratt.⁷ The solution has the following composition: sodium metaphosphate (Merck), 2; sodium chloride, 0.9; distilled water, 100.

In my experience, this solution has proved most satisfactory. It appears to keep almost indefinitely and rarely becomes contaminated with molds or bacteria. It has been kept without deterioration for over a year. In this preserving fluid, the platelets and erythrocytes are excellently preserved. The formation of "Arnold bodies" from erythrocytes is seen only in older preparations, and such bodies can be easily identified and differentiated from platelets when the oil immersion lens is employed. In this solution, the platelets appear as clear, highly refractile bodies surrounded by a halo of fine radiating lines. At times, they vary considerably in size, from one-fourth to one-half the diameter of a red cell. The smaller platelets are probably the younger ones.³ If the preparation has been properly made, the platelets and erythrocytes

4. Rees, H. M., and Ecker, E. E.: An Improved Method for Counting Blood Platelets, *J. A. M. A.* **80**:621 (March 3) 1923.

5. Buckman, T., and Hallisey, J. E.: Studies in Properties of Blood Platelets, *J. A. M. A.* **76**:427 (Feb. 12) 1921.

6. Wright, J. H., and Kinnicutt, R.: A New Method for Counting Blood Platelets for Clinical Purposes, *J. A. M. A.* **56**:1457 (May 20) 1911.

7. Pratt, J. H.: A Critical Study of the Various Methods Employed for Enumeration of Blood Platelets, *J. A. M. A.* **45**:1999 (Dec. 30) 1905.

were given by the authors. By my technic, comparative counts yielded figures as shown in table 4.

4. Tyrode's Solution.¹⁴ This solution, which is a good artificial nourishing fluid, has the following composition: Na CL 8; KCL 0.2; Ca Cl₂ 0.1; NaH₂PO₄ 0.05; NaHCO₃ 1; dextrose 1; oxygen to saturation, and H₂O 1,000.

Flössner¹⁵ modified this solution by omitting the dextrose and oxygen and adding mercuric chloride in the proportion of 5 parts of Tyrode's solution to 1 part of a 1 per cent solution of mercuric chloride. Flössner's modification of Tyrode's solution is a good preservative, much better for erythrocytes, however, than for platelets. The latter are preserved for about twenty minutes; then they begin to disintegrate

TABLE 4.—Platelet Counts When the Author's Technic was Used with Rees and Ecker's Solution

Person	Sex	Age	Platelets per Cubic Millimeter		Remarks
			Pratt's Solution	Rees and Ecker's Solution	
58	M	58	969,000	507,000	Normal
59	M	23	437,000	259,000	Chronic secondary anemia
60	F	40	534,000	343,000	Normal

TABLE 5—Normal Platelet Counts When the Author's Technic was Used with Flössner's Solution

Person	Sex	Age	Platelets per Cubic Millimeter	
			Pratt's Solution	Flössner's Solution
46..	M	30	796,000	261,000
47..	M	29	979,000	278,000
48..	M	27	652,000	405,000
49..	M	28	662,000	197,000

into rather coarse refractile granules. I found both Tyrode's original solution and Flössner's modified Tyrode's solution inferior to the solution of sodium metaphosphate. They have the added disadvantage of being much more complicated in composition. By employing the indirect method and a counting chamber, a procedure involving considerable error, Flössner¹⁵ and Hoffmann¹⁶ found that the average number of platelets per cubic millimeter based on seventy-five counts from twenty-five normal persons was 760,000 in men and 682,000 in women; the

14. Tyrode, M. V.: The Mode of Action of Some Purgative Salts, Arch. internat. de pharmacod. et de thérap. **20**:205, 1910.

15. Flössner, O.: Beobachtungen und Zählung von Blutplättchen, Ztschr. f. Biol. **77**:113, 1922-1923.

16. Hoffmann, F. B.: Ueber Blutplättchenzählung, Deutsche med. Wchnschr. **52**:861 (May 21) 1926.

study,¹² the mean of five counts on five consecutive days on the same person was 457,000 platelets per cubic millimeter. The high counts of these investigators were undoubtedly due to the inclusion in the platelet count of large numbers of "Arnold bodies." By employing my technic, which will be discussed later, I obtained comparative counts with Kemp and Calhoun's solution, as shown in table 2.

2. Fonio's solution.¹³ This is a 14 per cent solution of magnesium sulphate. It is highly hypertonic, as seen from the crenated and shrunken appearance of the erythrocytes. Most preparations showed numerous artefacts in the form of "Arnold bodies." The preparations contained remarkably few small platelets, which were undoubtedly destroyed. Fonio employed the indirect method. By means of dry

TABLE 2.—*Normal Platelet Counts When the Author's Technic was Used with Kemp and Calhoun's Solution*

Person	Sex	Age	Platelets per Cubic Millimeter	
			Pratt's Solution	Kemp and Calhoun's Solution
46.....	M	30	796,000	278,000
47.....	M	29	979,000	449,000
48.....	M	27	652,000	208,000
49.....	M	28	662,000	224,000

TABLE 3.—*Normal Platelet Counts When the Author's Technic was Used with Fonio's Solution*

Person	Sex	Age	Platelets per Cubic Millimeter	
			Pratt's Solution	Fonio's Solution
55.....	M	28	765,000	404,000
56.....	F	22	741,000	276,000
57.....	F	40	614,000	468,000

preparations, he obtained average counts of 234,231 platelets per cubic millimeter. Comparative counts by my technic yielded results as shown in table 3.

3. Rees and Ecker's solution.⁴ This solution consists of 3.8 per cent sodium citrate, 0.2 per cent formaldehyde and 0.1 per cent brilliant cresyl blue. The platelets and the red cells were not well preserved in this solution; the erythrocytes frequently appeared crenated, with many artefacts ("Arnold bodies") attached to them. The preparations frequently contained a fine precipitate that obscured the field. No figures

12. Kemp, G. T.: Relation of Blood Plates to the Increase in Number of Red Corpuscles at High Altitudes, *Am. J. Physiol.* **6**:11, 1902.

13. Fonio, A.: Ueber ein neues Verfahren der Blutplättchenzählung, *Deutsche Ztschr. f. Chir.* **117**:176 (June) 1912.

chambers with smaller depths are employed, methods involving their use are unreliable (Pratt,⁷ Helber²⁰).

THE AUTHOR'S PROCEDURE

In order to avoid the use of the graduated pipet and of the counting chamber, I employed the indirect method so modified that the freshly drawn blood comes in contact with only paraffin-coated surfaces. A drop of freshly drawn blood is transferred to a paraffin cup filled with the preserving fluid. A few small drops of the diluted blood are then placed on a cleaned glass slide and covered with a cover slip, and the ratio of the platelets to the red cells is determined. The number of erythrocytes is then counted with the ordinary Thoma-Zeiss apparatus.

Slides are placed first in strong sulphuric acid saturated with potassium bichromate, and are kept there from twenty-four to seventy-two hours; they are then washed in water and alcohol and placed in jars containing 95 per cent alcohol. They are removed from the alcohol and wiped dry immediately before use. The glassware must be scrupu-

TABLE 6.—*Comparison of the Platelet Counts of Blood from Finger and from Ear*

Person	Platelets per Cubic Millimeter	
	Finger	Ear
42.....	578,000	392,000
50.....	711,000	693,000
51.....	492,000	472,000
52.....	603,000	512,000

lously clean, for, as Fenn²¹ showed, hemolysis is most marked on slightly soiled glass and may occur so rapidly with unfixed cells that accurate counts are rendered impossible. When hemolysis occurs, artefacts in the form of "Arnold bodies" nearly always appear.

The site from which the blood is to be drawn must be thoroughly cleaned with soap and water and then with alcohol and ether immediately before the puncture is done. More elaborate preparation of the skin is unnecessary. In order to avoid contact of the freshly drawn blood with the skin, I have attempted to cover the site of the puncture with some inert substance and to puncture through it. Paraffin, paraffin dissolved in xylene and collodion dissolved in ether were tried, but the counts obtained were so unsatisfactory that I abandoned this additional procedure. Aynaud,²² Buckman and Hallisey,⁵ Kristenson²³ and others

20. Helber, E.: Ueber die Zählung der Blutplättchen im Blute des Menschen und ihr Verhalten bei pathologischen Zuständen, *Deutsches Arch. f. klin. Med.* **81**:316 (Sept.) 1904.

21. Fenn, W. O.: Hemolysis of Erythrocytes in Contact with Glass; *J. Exper. Med.* **35**:271 (Feb.) 1922.

22. Aynaud, M. N.: *Le globulin des mammifères*, Med. diss., Paris, 1909.

23. Kristenson, A.: A New Method for the Direct Counting of Blood Platelets, *Acta med. Scandinav.* **57**:301, 1922.

maximum being 907,000 and the minimum 636,000. Table 5 shows the comparative counts obtained by the technic described in this paper.

ERRORS IN THE USE OF THE GRADUATED PIPET

The tendency of the platelets to adhere to glass and other foreign substances has been overlooked or disregarded by many in selecting a method for counting platelets. Halla,¹⁷ Muir¹⁸ and other early investigators recognized the fallacy of employing the graduated pipet. It is significant that, as a rule, when the capillary pipet was used by investigators the counts were lower than when some other method was employed which obviated the loss of platelets through their adherence to the sides of the pipet. This error, as Pratt⁷ has shown, may amount to 50 per cent. The objections to the use of the graduated pipet have been emphasized by nearly all investigators of the subject, and those who have used it have pointed out that while the results are only approximately accurate, they are still of value. One variable factor in the error of this method is the temperature of the pipet, as has been recognized by Hayem¹⁰ and by Kemp, Calhoun and Harris;¹⁹ in a warm room, the error would be greater than in a cold room. No method, therefore, can be regarded as trustworthy, which involves the use of the graduated pipet.

ERRORS IN THE USE OF THE COUNTING CHAMBER

Many investigators have recognized that in the ordinary counting chamber foreign bodies might easily be mistaken for platelets; hence the unreliability of counts made in this manner. Even when the dry high power lens is used, products of degenerated erythrocytes ("Arnold bodies"), foreign particles and bacteria may be mistaken for platelets. The platelets themselves, particularly the small forms, are often recognized with difficulty in the chamber. Another objection to this procedure is the depth of the chamber, as was pointed out by Pratt,⁷ Halla¹⁷ and others. The ordinary Thoma-Zeiss chamber is 0.1 mm. or 100 microns deep, which is more than fifty times the diameter of the average platelet. The erythrocytes quickly settle to the bottom, but the platelets, being considerably lighter in weight, tend to float in the upper layers of the fluid and do not all settle to the bottom. It is therefore difficult not to miss some of them in the count. Even when specially constructed

17. Halla, A.: Ueber den Haemoglobingehalt des Blutes und die quantitativen Verhältnisse der rothen und weissen Blutkörperchen bei acuten fieberhaften Krankheiten, *Ztschr. f. Heilk.* **4**:331, 1883.

18. Muir, R.: Contributions to the Physiology and Pathology of the Blood, *J. Anat. & Physiol.* **25**:256 (Jan.) 1891.

19. Kemp, G. T.; Calhoun, H., and Harris, C. E.: The Blood Plates, Their Enumeration in Physiology and Pathology, *J. A. M. A.* **46**:1022 (April 7) 1906.

and sealed with petrolatum. Two preparations should always be made, and if the ratio of platelets to erythrocytes varies markedly in the two, new specimens should be prepared. An oil immersion lens should be used. A square diaphragm in the ocular facilitates counting; this can be made from thick paper or a card, and forms a simple substitute for Ehrlich's ocular. The platelets and erythrocytes are both counted in fields taken at random in different parts of the specimen, until at least from 250 to 500 red cells in each of the two preparations have been seen. A red cell count is then done in the usual manner, and the absolute number of platelets per cubic millimeter is determined.

Table 7 represents the platelet counts obtained by this method on forty-four normal persons, thirty-one males and thirteen females.

The minimum count in this group was 407,000 platelets per cubic millimeter; the maximum, 1,108,000. The average for the group was

TABLE 8.—*Variation of the Platelet Count of the Normal Adult*

Adult	Sex	Age	Date (1928)	Platelets per C.Mm.	Average	Percentage of Variation
1	M	27	June 20 Oct. 24	705,000 711,000	708,000	0.8
2	M	30	Aug. 6 Aug. 15	539,000 540,000	539,500	0.2
3	M	30	Aug. 2 Aug. 22	741,000 662,000	701,500	11.2
4	M	34	Aug. 10 Aug. 13	478,000 433,000	455,500	9.9
5	F	42	Sept. 28 Oct. 31	566,000 578,000	572,000	2.0

619,000 platelets per cubic millimeter; the average for males was 650,000; that for females was 587,000.

I observed that when the platelet count is below 500,000 per cubic millimeter, the platelets tend to be of the large or adult variety. This observation was also made by Boshamer.³ In no. 8, whose platelet count was 407,000, the individual platelets were unusually large. The higher platelet counts of normal persons are due to the presence of numerous small forms, and it is probable that in these persons there is an unusually active formation of platelets.

In order to determine the variation of the platelet count of the same person, I made counts of blood from five healthy adults on different days, as shown in table 8.

In view of the physical properties of the platelets, particularly their fragility and light weight, it appears to me that differences up to 10 per cent or even 15 per cent should be considered as within the permissible errors of the method employed. The average percentage of variation in the group mentioned was 4.8 per cent.

recommended venipuncture, because by this procedure adhesion of platelets to raw surfaces and admixture of tissue juices are avoided. Besides being more inconvenient, this method does not yield higher counts than the methods in which capillary blood is used. Zeller²⁴ concluded from careful comparative studies that venous blood gives lower platelet counts than capillary blood. Because of the simplicity and the ease with which it is carried out, I have employed the method of simply stabbing the finger or lobe of an ear with a clean, sharp needle. The puncture should always be made sufficiently deep to cause the blood to flow freely without applying any pressure. The application of pressure adjacent to the puncture wound must always be avoided, as this procedure may reduce the normal platelet count to one-half its

TABLE 7.—*Normal Platelet Counts by the Author's Method*

Person	Age	Platelets per C.Mm.	Person	Age	Platelets per C.Mm.
MALES					
1.....	33	502,000	38.....	17	453,000
2.....	30	506,000	41.....	15	672,000
3.....	32	717,000	43.....	55	531,000
5.....	30	673,000	44.....	24	776,000
6.....	27	705,000	45.....	35	598,000
8.....	27	407,000	46.....	34	796,000
9.....	35	699,000	47.....	30	979,000
10.....	35	614,000	48.....	27	652,000
19.....	35	414,000	49.....	30	662,000
20.....	69	668,000	50.....	27	711,000
21.....	30	571,000	51.....	55	492,000
29.....	30	741,000	52.....	25	603,000
30.....	30	539,000	54.....	58	1,108,000
32.....	32	431,000	55.....	28	765,000
33.....	34	478,000	58.....	58	969,000
37.....	35	733,000			
FEMALES					
11.....	36	491,000	27.....	42	566,000
15.....	16	715,000	42.....	42	578,000
17.....	60	450,000	56.....	22	741,000
18.....	72	569,000	57.....	40	614,000
24.....	66	706,000	60.....	40	534,000
25.....	36	439,000	61.....	42	581,000
26.....	14	691,000			

value. Blood obtained from the fingertip gives higher platelet counts than blood obtained from the lobe of an ear, as shown in table 6.

Two or three large drops of the sodium metaphosphate solution are placed in a small paraffin cup. The cup can be prepared by melting the center of a small cube of paraffin, about 2 cm. on the side, with the heated end of a glass rod. A small drop of freshly drawn blood is allowed to fall into this solution, producing a dilution of approximately 1:10. This is gently stirred once or twice with an ordinary wooden applicator, the end of which is coated with paraffin. A few small drops or one large one of this mixture is transferred by means of the wooden applicator to a cleaned glass slide, covered with a cleaned cover slip

24. Zeller, H.: Neue Methode der Blutplättchenzählung nebst einigen Resultaten, Ztschr. f. d. ges. exper. Med. 10:103, 1919-1920.

SUMMARY

An improved indirect method for the enumeration of platelets is described. It adheres to the leading principles that must be taken into consideration in counting platelets: (1) avoidance of contact between the undiluted blood and glassware or metal, (2) mixing of the freshly drawn blood as quickly as possible with the preserving fluid and (3) avoidance of all unnecessary manipulations of the blood. It dispenses with the use of the graduated pipet and counting chamber. It eliminates the errors resulting from the inclusion in the platelet count of degeneration products of erythrocytes ("Arnold bodies") and of finely particulated foreign matter. The results obtained are higher than ever previously obtained by similar methods.

Moderately high platelet counts were previously obtained by investigators as follows: Prus,²⁵ 500,000; Puchberger,²⁶ 600,000; Brodie and Russell,²⁷ 635,000; Zeller,²⁴ 635,000; Flössner,¹⁵ 760,000; Sooy and Laurens,²⁸ from 762,000 to 863,000; Kemp and Calhoun,²⁹ 778,00 and 862,000. All these investigators, however, employed methods involving the use of either the graduated pipet or the counting chamber or of both. Their results are therefore untrustworthy. Zeller's method involves the use of a paraffin cup and torsion weights, a procedure not well adapted for clinical purposes. The results that can be considered as trustworthy are those obtained by the indirect methods for the enumeration of blood platelets and based on the determination of the erythrocyte-platelet ratio in fresh preparations, thereby obviating the necessity of the graduated pipet and of the counting chamber. Such methods were employed by Pratt,⁷ von Boros and Kalstein³⁰ and Jedlička and Altschuller.³¹ Their results are, however, lower than mine. Pratt,⁷ who originally used the sodium metaphosphate-sodium

TABLE 9.—*Comparison of the Platelet Counts Done by the Author's and by Pratt's Technic*

Person	Sex	Age	Platelets per Cubic Millimeter	
			Author's Technic	Pratt's Technic
62.....	F	9	556,000	353,000
63.....	M	29	570,000	440,000
64.....	M	26	661,000	398,000

chloride solution employed in this investigation, obtained average counts of 469,000 platelets per cubic millimeter. His technic, however, was different and consisted of a transference of the freshly drawn blood to some preserving fluid on a glass slide by means of a sterilized platinum loop, filled with the same solution. Comparative studies done by the technic described here and by that of Pratt are shown in table 9.

25. Prus, J.: Einiges über das Verhalten des leukämischen Blutes, *Medycyna*, 1886, nos. 39 and 40; abstr., *Centralbl. f. klin. Med.* **8**:469 (June 18) 1887.

26. Puchberger, G.: *Wien. med. Wchnschr.* **55**:1402, 1905.

27. Brodie, T. G., and Russell, A. E.: The Enumeration of Blood Platelets, *J. Physiol.* **21**:390 (May 12) 1897.

28. Sooy, J. W., and Laurens, H.: A Method for Counting Blood Platelets, *Proc. Soc. Exper. Biol. & Med.* **22**:116, 1924.

29. Kemp and Calhoun (footnotes 8 and 11).

30. Von Boros, J., and Kalstein, O.: Ein Beitrag zur Frage der Blutplättchen-zählung, *Folia haemat.* **35**:419, 1928.

31. Jedlička, V., and Altschuller, G.: Chronic Essential Thrombopenia, *Acta med. Scandinav.* **64**:123, 1926.

the peritoneum, were edematous and grayish, and enlarged mesenteric lymph nodes with no microscopic peculiarity were found in several cases. A careful search revealed in our patient only one parathyroid gland that was normal. No distinctive pathologic process was observed.

The earliest symptom has usually been diarrhea (twenty-five cases). Two patients complained first of weakness, two of loss of weight, three of a sore mouth, and one of fatigue. The diarrhea has almost always been characteristic for sprue, with large, frothy, grayish stools occurring some time in the course of the disease. The diarrhea frequently occurs in the early morning hours. Constipation is present at times, as shown in one patient who entered our clinic with a history of sprue of nine years' duration. Recently, marked constipation had developed, but there were other well marked symptoms of sprue. At some time all the patients had trouble with the mouth, consisting of definite small ulcers in most cases. Several complained of a severe burning sensation in the mouth, and in two cases there occurred a dry mouth, in one of which ulcers did not develop until three years after the first entry to the hospital. All of them complained of marked abdominal distention with much gas during the course of the disease, and two complained of severe burning of the stomach. One of these patients was successfully treated with daily lavage of the stomach, but in the other patient it was a difficult condition with which to deal. Eighteen patients gave histories of more or less tingling and numbness of the hands and feet, while four had definite signs of tetany. All the patients gave histories of weakness and of more or less loss of weight during the acute process.

There is nothing of particular interest in the previous illnesses of these patients except that five gave a history of amebic dysentery and four of malaria contracted during their stay in the tropics. Usually, after careful questioning, it was found that the diagnosis of dysentery or malaria was made at the onset of sprue, and this made it difficult to differentiate the symptoms of the conditions. These diagnoses of amebic dysentery and malaria were not verified at the time of the acute condition and often there was no typical history, such as bloody stools or typical chills and fever; hence we believe that probably these indicated only the onset of sprue.

Physically, these patients usually showed a considerable loss of weight, sallow skin, low blood pressure and a distended abdomen with a thin abdominal wall. Frequently the large bowel could be palpated, but the liver was not palpable nor was it especially small when carefully examined. In four cases the patients gave positive tetany reactions—Trousseau's and Chvostek's signs or tetany spasms. Ulcers of the mouth were seen frequently, appearing as small, white areas of from 2 to 3 mm. in width with reddened areas around them. These ulcers

were carried out in many of our cases (thirty), and low values were found in eleven. In seven of these, the blood calcium was only slightly below normal (8.1 to 8.6), but in four the abnormality was marked. In one patient, while under observation, the blood calcium decreased from a normal to a markedly low figure, and with this decrease definite signs of tetany developed. The test for a toxic substance in the blood serum of patients with pernicious anemia, as developed by Macht,⁵ has been tried in ten of our cases of sprue, six of which showed a blood picture like that found in pernicious anemia, and three of these showed the toxic substance present. After marked improvement in one of these cases this toxic substance was not found. A negative reaction to the test was obtained in the four cases of secondary anemia.

Gastric fractional studies showed achlorhydria in seven cases. There was also a negative alkaline tide in two cases; we have accepted these as belonging in the same group. These two cases and five of the seven of achlorhydria occurred among patients with a blood picture like that in pernicious anemia; two of the patients with secondary anemia showed achlorhydria. In the two cases in which the patients complained of severe burning of the stomach, there were normal acid curves in the fractional test.

Roentgen-ray studies of the gastro-intestinal tract were made in twenty-nine cases; dilated, atonic, gas-filled colons were found in thirteen. The haustrations in these colons were large and often irregularly spaced with some greatly dilated areas in which haustrations were entirely absent. Another feature that was prominent in the late cases was the apparent elongation of the colon; it appeared to fill the abdomen almost completely. The gas gave a peculiar mottled appearance to the colon as if it were mixed with the contents of the intestines, and there were often linear streaks of barium sulphate along the wall resembling those that are frequently seen in patients with colitis. The earlier cases of sprue showed these changes in a very mild degree or else not at all, but in the late cases the changes were exceedingly marked. We have also noticed that hypermotility often exists, with the head of the barium column reaching the lower part of the large bowel in a few hours, but in spite of this, some of the barium may remain in the colon for many days at a time. The advanced cases present such typical roentgen observations that one might almost suspect the presence of sprue from this factor alone, but in the earlier cases such studies give no clue to the presence of the disease.

5. Macht, D. I.: A Study of the Toxin of Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **23**:209, 1925; Pernicious Anemia, An Experimental Contribution to the Etiology, Diagnosis and Treatment, *J. A. M. A.* **89**:753 (Sept. 3) 1927.

were usually on the tongue, and sometimes the mucous membrane of the floor of the mouth or cheeks was involved. In one case a fiery inflammation of the mucosa of the mouth occurred while the patient was under observation. The loss of weight has been more than one fourth of the patient's average weight in fifteen patients, eleven of whom had severe anemia; of the four others with a history of severe loss of weight, one had a marked secondary anemia.

Various laboratory tests were carried out and frequently repeated. Examinations of the urine showed nothing particular, albumin, leukocytes and casts occurring in some specimens. The urobilogen and the urobilinogen were sometimes increased. Sugar was not found in any patient. The function of the kidney was impaired in the two oldest cases, but this condition improved under the diet high in protein.²

The feces were almost always characteristic of sprue during the acute process. One phase of our study of sprue has been the culture of stools for the monilia organism.³ In twenty-three cases we were able to grow a monilia which corresponded in all characteristics with Ashford's *Monilia psilosis*. In nine cases, a yeast organism was grown that was somewhat atypical. In only three cases were no monilia found, and in many positive cultures they were repeatedly obtained. The organism was grown from material taken from the tongue in one of six cases in which such cultures were made. It was grown from various parts of the digestive tract from material obtained at autopsy in one case.¹

In twelve cases there was a secondary anemia of more or less severe degree, and in eight cases the blood was normal. In sixteen there was a blood picture much like that found in pernicious anemia. In thirteen of these cases there were less than 3,000,000 red cells and in three there were less than 2,000,000. The color index was high, and there was a leukopenia. The percentage of lymphocytes was increased, that of the platelets decreased, and there were changes in the red cells such as poikilocytes, megalocytes and polychromatophilia. In these cases, however, we have rarely observed normoblasts, and megaloblasts were seen in only one.⁴

In the twenty-five patients tested, the blood sugar was normal, the blood urea and creatinine were disturbed only as the kidney was affected (nephritis, two cases); the blood cholesterol was normal in five cases, and the fatty acids possibly low in seven. Studies on the blood calcium

2. Baumgartner, E. A., and Hubbard, Roger S.: The Effect of High Protein Diet on Some Blood Constituents, *Clifton M. Bull.* **13**:52, 1927.

3. Baumgartner, E. A., and Smith, Glenn D.: The *Monilia Psilosis* as a Cause of Tropical Sprue, *Am. J. Trop. Med.* **6**:433, 1926.

4. Baumgartner, E. A., and Smith, Glenn D.: Pernicious Anemia and Tropical Sprue, *Arch. Int. Med.* **40**:203 (Aug.) 1927.

of blood, which is lower than the normal figures for blood calcium. We feel that the roentgen examination of the digestive tract may be of distinct value in differentiating these two conditions. The dilated, atonic colon with much gas, often with no evidence of haustrations, is found in sprue and in our experience has not been seen in pernicious anemia. In five of seven patients showing achlorhydria, roentgen studies of the gastro-intestinal tract were not done; but two showed the colon typical of sprue. In the accompanying table are listed four

Data in Cases of Sprue with Blood Picture of Pernicious Anemia

Length of Illness, Years	Reaction of Blood, Pernicious Anemia Type	Fractional Free Acid	Gastro-intestinal Series	Tetany	Blood Calcium	Outcome of Cases	Diagnosis, Pernicious Anemia
3	Positive	Negative at autopsy	Not done	Positive	5.2	Death from sprue	No
9	Positive	0	Not done	0	8.3	Well 5 years	?
4	Positive	26	Sprue	Positive	6.2	Mental 4 years	No
6	Positive	Negative tide	Sprue	Positive	7.3	Death 1 year, sprue	No
1	Positive	34	Sprue	0	11.0	Death 5 years, later pneumonia	No
4	Positive	0	Sprue	Positive	3.1	?	No
10	Positive	0	Not done	0	10.3	Well 5 years	?
2½	Positive	21	Not done	0	10.4	?	No
3	Positive	68	Sprue	0	9.6	Well 3 years	No
2	Positive	47	Normal	0	10.7	Well 3 years	No
3	Positive	51	Normal	0	8.5	?	No
10	Positive	65	Sprue	0	8.6	Pneumonia, sprue 3 years	No
3	Positive	23	Sprue	0	10.0	?	No
3	Positive	34	Sprue	0	8.1	Well 1 year	No
1	Positive	0	Not done	0	10.8	Well 3 years	?
3	Positive	Negative tide	Not done	0	Not done	Well 2 years	?

cases in which we made the diagnosis of sprue but admit the possibility that they were cases of pernicious anemia. At times it is extraordinarily difficult, and even impossible to differentiate the two diseases, and we know of at least one patient who went through our clinic in the past five years with the diagnosis of pernicious anemia who undoubtedly had tropical sprue.

PROGNOSIS

Of the thirty-six patients whom we have considered, two were without symptoms and may be accepted as having arrested or "cured" cases for one and nine years. Five other patients had only mild symptoms, ten were moderately ill and nineteen were severely ill or completely incapacitated while under observation. One of the sixteen patients with a

DIAGNOSIS

From the preceding description of the history and physical examination we can see that when certain symptoms are present, the diagnosis of sprue is easy, but other cases occur in which the diagnosis may be difficult. In most cases the history of large, gray, frothy stools occurring in a patient having spent some time in the tropics should at least call to mind the possibility of sprue. If the diarrhea occurs in the early morning and is associated with sore mouth, weakness and loss of weight, sprue should be suspected. If, in addition to this, the abdomen is distended, small ulcers are present in the mouth, and there is a more or less severe anemia, the diagnosis of sprue may be made. Numbness and tingling may occur, but we have never found the neurologic signs of combined sclerosis such as those seen in pernicious anemia. In our experience, tetany and a low blood calcium, if they occur in cases showing such symptoms, make the diagnosis of sprue certain.

Two diseases, pancreatic deficiency and pernicious anemia, are especially likely to simulate sprue. Pancreatic disease may cause the large, gray foamy stools seen in patients with sprue, but the sore mouth does not occur, neither does one find the low blood calcium or a blood picture like that of severe pernicious anemia. Glycosuria, a not infrequent observation in pancreatic disease, was not seen once in our thirty-six cases of sprue. The differentiation between sprue and pernicious anemia is much more difficult; indeed, some authors, Wood ⁶ and Reed ⁷ among others, contend that they are one disease. The digestive disturbance, the sore tongue, the blood picture with megalocytes, the definite increase in the average size of the red blood cells such as Price-Jones found in pernicious anemia,⁸ and the neurologic symptoms are very confusing. However, our patients with pernicious anemia rarely have early morning diarrhea, never the characteristic stools seen in sprue, nor such severe loss of weight, and never a low blood calcium nor tetany reactions. Two of the sixteen patients with a blood picture like that found in pernicious anemia had hyperchlorhydria. Only seven of the sixteen cases showed achlorhydria (two showed negative alkaline tides and were accepted as having achlorhydria). Three of these and also one with a normal hydrochloric acid content on fractional examination showed low blood calcium with tetanic reactions. One other patient with achlorhydria had 8.3 mg. of calcium per one hundred cubic centimeters

6. Wood, E. J.: Pernicious Anemia in Its Relationship to Sprue, *Am. J. M. Sc.* **159**:28, 1925.

7. Reed, A. C., and Wyckoff, H. A.: The Common Picture of Sprue, Pernicious Anemia, and Combined Degeneration, *Am. J. Trop. Med.* **6**:221, 1926.

8. Price-Jones, C.: Anisocytosis with Special Reference to Pernicious Anemia, *Guy's Hosp. Rep.* **74**:10, 1924.

this case could belong to Ashford's hypoplastic type of anemia. In one case with low blood calcium, Collip's parathyroid extract was given,¹² and in two others $\frac{1}{10}$ grain (0.00648 Gm.) of the dry extract and 10 grains (0.648 Gm.) of calcium lactate, three times daily. In all of these patients the blood calcium quickly became normal, and the tetanic reactions disappeared. In one patient, however, who died one week after observation, the dry extract had no apparent effect as the blood calcium at autopsy was 5.6 mg. per hundred cubic centimeters of blood, which is about as it was at the onset of treatment. Another patient responded rather slowly to the administration of parathyroid (dry), but several months after leaving she did not respond at all to the intravenous injection of calcium chloride. Bovaird's patient, described by Barach and Murray,¹³ also did not respond to intravenous injections of calcium. Details of the third case in our series, in which the patient died of pneumonia (and sprue), are not available. We wonder whether tetanic reactions might have been found, although during almost three years' observation of this patient, the blood calcium was only once found to be low (8.6 mg.), and there was no history of neurologic symptoms. Patients with achlorhydria, as well as those with pernicious anemia, are given dilute hydrochloric acid. This drug is quite difficult to take at times when ulcers or sore mouth are present. Pancreatic extract¹⁴ has been given to several patients without any apparent effect. Transfusions have been used with good results when they were indicated.

SUMMARY

Thirty-six cases diagnosed as sprue have been reviewed. In sixteen of these the blood picture was similar to that in pernicious anemia; in all but four the condition could be conclusively shown not to be pernicious anemia (Addison), because free hydrochloric acid was found in the stomach, a low blood calcium with or without tetanic reactions was present, or a definitely large dilated colon occurred, which we believe is a characteristic of sprue and is not found in pernicious anemia. Several cases showed a severe secondary type of anemia. Improvement in the general physical condition with a definite return of the appetite almost always occurs with a restriction of carbohydrates and fats in the diet. Liver is valuable as treatment in the severely anemic cases frequently found.

12. Baumgartner, E. A.: Parathyroid in the Treatment of Tropical Sprue, *Am. J. Trop. Med.* **7**:181, 1927.

13. Barach, A. L., and Murray, H. A.: Tetany in a Case of Tropical Sprue, *J. A. M. A.* **74**:786 (March 20) 1920.

14. Brown, T. R.: Absence of Pancreatic Secretions in Sprue and Employment of Pancreatic Extract in Treatment of This Disease, *Am. J. M. Sc.* **161**:501, 1921.

blood picture like that found in severe pernicious anemia, died one week after entry, following a slight cold and pleurisy. Another patient left after several months' treatment with little if any improvement. Five months later this patient died with tetany spasms, evidently from sprue. In two severe cases, after improving markedly here, the patients died elsewhere from pneumonia, one five years, the other three years after his first entry here. Both of these had responded well to treatment, regaining weight and showing a normal blood picture, but both had relapses, from which one was again recovering, while the other showed no improvement in any of his symptoms. According to recent reports, eight of the remainder of the group of sixteen have been well physically for from one to four years, although one had a relapse two years ago from which she has again recovered. Four patients had not been heard from. In the other cases, it is reported that one patient died of a cancer of the digestive tract, six have not been heard from for two years, and the remainder have been well for from one to three years after discharge. One of the latter had a severe relapse but again recovered.

In the entire group only two patients failed to respond definitely and markedly to treatment. Three patients returned with exacerbations of some symptoms, but all responded to a more restricted diet than they had been using at home. Bastedo and Famulener,⁹ in their study of sprue, described two patients who died of severe anemia and a color index of 1+. Reed stated that patients with sprue rarely recover.

TREATMENT

Our treatment for sprue has been mainly by a diet high in protein and low in fat and carbohydrates. Since Minot and Murphy's liver diet for pernicious anemia was described, we have used liver in some cases.¹⁰ In our experience as well as in that of others liver has been as efficacious in the control of the anemia in cases of sprue as it has been in cases of pernicious anemia. Ashford¹¹ before the International Association of Tropical Medicine last year described some cases as being refractory to treatment with liver. One of our patients recently succumbed while under care in another hospital without having made any recovery in blood count, although three years previously he had gained from 2,000,000 to 4,800,000 erythrocytes in our clinic. Possibly

9. Bastedo, W. A., and Famulener, L. W.: *Tropical Sprue*, J. A. M. A. **81**:2102 (Dec. 22) 1923.

10. Rabe, Helen; and Baumgartner, E. A.: *Diet in Tropical Sprue*, Clifton M. Bull. **14**:55, 1928.

11. Ashford, B. K.: *Suggestions for a Rapid Classification of the Anemias of Sprue*, Porto Rico J. Pub. Health & Trop. Med. **5**:167, 1929.

sis. It was the purpose in the experiments reported in this paper to study this aspect of the arteriovenous difference.

The tests consisted in the administration of 1.75 Gm. of dextrose per kilogram of body weight to patients without food for the preceding fifteen hours and confined to their beds, except in a few cases, for the duration of the test. A moderate quantity (from 400 to 800 cc.) of water was consumed during the period of observation. Capillary (arterial) blood from the finger pad and venous blood from the cubital vein

TABLE 1.—*Normal Persons: Sugar Content of Capillary and Venous Blood Following a Standard Dextrose Meal*

No.	Origin of Blood	Before Administration of Dextrose		After the Administration of Dextrose							
				½ Hour		1 Hour		2 Hours		3 Hours	
		Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference
1	Arterial.....	101		173		158		128		110	
	Venous.....	88	+13	114	+59	100	+58	100	+28	84	+26
2	Arterial.....	83		180		113		115		77	
	Venous.....	81	+ 2	130	+50	97	+16	98	+17	71	+ 6
3	Arterial.....	80		105		113		93		69	
	Venous.....	72	+ 8	83	+22	65	+48	56	+37	57	+12
4	Arterial.....	80		152		133		115		106	
	Venous.....	74	+ 6	104	+48	98	+35	83	+32	73	+33
5	Arterial.....	75		138		102		127		101	
	Venous.....	82	— 7	113	+45	122	+ 5	95	+ 6
6	Arterial.....	94		166		132		121		99	
	Venous.....	88	+ 6	138	+28	122	+30	83	+39	86	+13
7	Arterial.....	69		159		182		134		45	
	Venous.....	64	+ 5	135	+24	161	+21	111	+23	40	+ 5
8	Arterial.....	83		154		154		139		106	
	Venous.....	89	— 6	150	+ 4	135	+19	96	+10
9	Arterial.....	93		154		207		178		120	
	Venous.....	94	— 1	144	+10	192	+15	166	+12	103	+17
10	Arterial.....	81		154		216		198		131	
	Venous.....	80	+ 1	138	+16	184	+32	168	+30	106	+25
11	Arterial.....	84		176		207		121		67	
	Venous.....	90	— 6	160	+16	172	+35	97	+24	52	+15
12	Arterial.....	82		126		150		116		95	
	Venous.....	79	+ 3	98	+28	107	+43	77	+39	60	+25

were obtained simultaneously before and at intervals after the administration of the dextrose. The true (fermentable) sugar (as distinguished from the total reducing substances) was determined according to Somogyi's (1929) technic. The figures given in the tables represent averages of three parallel determinations which agreed within ± 6 mg. per hundred cubic centimeters.

Table 1 comprises twelve cases considered as normal, because from the history and the physical and laboratory examinations, no evidence of disturbed carbohydrate metabolism was discovered. An analysis of the figures discloses the following facts: 1. In fasting, there were but

THE ARTERIOVENOUS DIFFERENCE IN BLOOD SUGAR CONTENT *

B. Y. GLASSBERG, M.D.

ST. LOUIS

Since Claude Bernard ¹ in 1877, Otto ² in 1885 and Pavy ³ in 1894 showed that there is a difference in the sugar content of arterial and venous blood, greater during digestion, a number of workers have studied this aspect of sugar metabolism. There is general agreement that in the fasting state the arterial blood contains from 3 to 5 mg. per hundred cubic centimeters more sugar than the venous, and that after the administration of dextrose this difference is increased to between 20 and 80 mg. Lawrence ⁴ and Rabinowitch ⁵ found that in the patient with diabetes, the arteriovenous difference is very much reduced; in fact, in some cases the sugar in the venous blood is higher than in the arterial. Friedenson ⁶ gave a good historical review of the entire subject. It is obvious that the arteriovenous difference is due to the fact that the peripheral tissues, especially the muscles, either store or burn part of the dextrose that passes through them. Since Foster ⁷ showed that arterial blood and capillary blood are identical in sugar content, it is easy to determine the amount of dextrose removed from the circulating blood by measuring simultaneously the sugar content of capillary and venous blood. In this manner, probably information of important diagnostic value could be obtained; that is, information showing whether or not the peripheral tissues are able to metabolize dextrose in a normal manner. Yet a survey of the literature shows that there has been little effort to utilize the arteriovenous difference as an aid in clinical diagno-

* Submitted for publication, March 28, 1930.

* From the Medical Service of the Jewish Hospital.

1. Bernard, Claude: *Leçons sur le diabète*, Paris, J. B. Baillière et fils, 1877, p. 237.

2. Otto, J. B.: *Ueber der Gehalt des Blutes an Zucker und reducierender Substanz und verschiedenen Umständen*, *Pflüger's Arch. f. d. ges. Physiol.* **35**:495, 1885.

3. Pavy, F. W.: *Physiology of the Carbohydrates*, London, J. & A. Churchill, 1894, p. 168.

4. Lawrence, R. D.: *Effect of Insulin on the Sugar Content of Arterial and Venous Blood in Diabetics*, *Brit. M. J.* **1**:516, 1924.

5. Rabinowitch, I. M.: *Simultaneous Determination of Arterial and Venous Blood Sugar in Diabetic Individuals*, *Brit. J. Exper. Path.* **8**:76, 1927.

6. Friedenson, W.; Rosenbaum, M. K.; Thalheimer, E. J., and Peters, J. P.: *Cutaneous and Venous Blood Sugar Curves*, *J. Biol. Chem.* **80**:269, 1928.

7. Foster, G. L.: *Studies on Carbohydrate Metabolism*, *J. Biol. Chem.* **55**:291, 1923.

venous difference was reached at one hour. However, the difference was prolonged, still being considerable at the three hour period, an observation not incompatible with that observed in the normal cases. In case 4, diagnosed as hypopituitarism, the maximal height of the venous sugar was reached in one hour, while the maximum arteriovenous difference was attained only after two hours and was maintained into the third hour. Cases 5 (chronic myocarditis) and 6 (duodenal ulcer) were examined, because it was thought that they would show a normal sugar metabolism. Surprisingly, the third hour level failed to drop to the fasting level. Case 5 showed a decided fluctuation in the arteriovenous difference, which was still high at the third hour. Case 6 showed an increasing arteriovenous difference, which was highest at the

TABLE 3.—*Diabetic Persons: Sugar Content of Capillary and Venous Blood Following a Standard Dextrose Meal*

No.	Origin of Blood	Before Administration of Dextrose		After the Administration of Dextrose							
				$\frac{1}{2}$ Hour		1 Hour		2 Hours		3 Hours	
		Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference
1	Arterial.....	101		172		193		200		181	
	Venous.....	93	+ 8	156	+16	173	+24	176	+24	152	+29
2	Arterial.....	128		221		290		262		158	
	Venous.....	136	- 8	226	- 5	264	+26	255	+ 7	151	+ 7
3	Arterial.....	321		391		400		456		507	
	Venous.....	306	+15	369	+22	399	+ 1	441	+15	498	+ 9
4	Arterial.....	224		329		382		454		392	
	Venous.....	222	+ 2	316	+13	376	+ 6	437	+17	400	- 8
5	Arterial.....	172		294		368		422		430	
	Venous.....	173	- 1	292	+ 2	374	- 6	414	+ 8	435	- 5
6	Arterial.....	236		317		450		506		452	
	Venous.....	229	+ 6	321	- 4	449	+ 1	513	- 7	447	+ 5

second and third hours. In case 7, diagnosed as chronic malnutrition, both the arterial and the venous curves rose and fell slowly. The rather low arteriovenous difference persisted practically unchanged over the entire three hour period.

It is obvious in this group of cases, too, that the blood sugar curve obtained with capillary blood cannot be interpreted on the basis of so-called standard curves obtained with venous blood. It is also seen in the three cases of hypothyroidism that there is no curve characteristic of the condition, based either on arterial or venous blood sugar or on the arteriovenous difference.

The six cases given in table 3 are those of patients with diabetes. The most conspicuous fact disclosed by these figures is that, in conformity with Rabinowitch's data, the arteriovenous difference was con-

slight differences between the sugar content of arterial and of venous blood. 2. The arteriovenous difference rises and recedes parallel with the blood sugar levels; its maximum occurs at the peak of the sugar curve thirty minutes after the ingestion of sugar in cases 1, 2, 4, 5 and 7, and at the one hour period in cases 3, 8, 9, 10, 11 and 12. Case 6 is the sole exception in which the maximal difference appeared two hours after the dextrose meal, whereas the sugar curve had risen to its peak in thirty minutes. 3. The maximum arteriovenous difference lies between 20 and 60 mg. per hundred cubic centimeters of blood. 4. These figures also disclose a fact of immediate practical significance; namely, that the blood sugar curves obtained from capillary blood cannot and

TABLE 2.—*Diseased Nondiabetic Persons: Sugar Content of Capillary and Venous Blood Following a Standard Dextrose Meal*

No.	Diagnosis	Before Administration of Dextrose		After the Administration of Dextrose							
				$\frac{1}{2}$ Hour		1 Hour		2 Hours		3 Hours	
		Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference	Mg. True Sugar per 100 Cc. of Blood	Difference
1.	Hypothyroidism	Arterial 79		147		165		126		99	
	Venous 75		+ 4	124	+23	128	+37	117	+ 9	84	+15
2.	Hypothyroidism	Arterial 84		160		177		164		123	
	Venous 77		+ 7	126	+34	137	+40	124	+40	89	+34
3.	Hypothyroidism	Arterial 84		142		200		131		106	
	Venous 84		\pm 0	133	+ 9	174	+26	124	+ 7	78	+28
4.	Hypopituitarism	Arterial 93		159		175		112		121	
	Venous 93		\pm 0	156	+ 3	162	+13	88	+24	97	+24
5.	Chronic myocarditis	Arterial 85		167		193		169		146	
	Venous 80		+ 5	154	+13	175	+18	167	+ 2	127	+19
6.	Duodenal ulcer	Arterial 87		245		299		192		138	
	Venous 92		- 5	221	+24	279	+20	160	+32	106	+32
7.	Malnutrition	Arterial 96		152		187		157		151	
	Venous	139	+13	165	+22	134	+23	128	+23

should not be substituted indiscriminately for venous curves. At present, in the possession of several good micromethods for sugar determination, one is much inclined to avoid the inconveniences of five venipunctures, and instead to draw but a few drops of capillary blood from the finger tip. Considering the possible arteriovenous differences at the end of the curve, it is obvious that the application of standards based on figures of venous blood might lead to confusion if applied to results obtained from capillary blood.

In table 2 are presented the experiments in seven nondiabetic cases in which either various endocrine dysfunctions were diagnosed clinically or disturbed carbohydrate metabolism was indicated by laboratory tests. The first three patients suffered from hypothyroidism. The peak of the curves was within normal limits, and in two cases the maximal arterio-

THE NATURE OF GRAVES' DISEASE *

ELI MOSCHCOWITZ, M.D.

NEW YORK

NOSOLOGY

Conventionally, Graves' disease is viewed as a disease in which the predominant signs and symptoms are tremor, tachycardia, enlargement of the thyroid gland and exophthalmos. Of lesser importance are loss of weight, diarrhea and sweating, pigmentation, a relative lymphocytosis and, in severe cases, fever and jaundice. It is generally agreed that such patients are "nervous," irritable and restless, and that they sleep poorly. As a rule, the disease is accompanied by an increased basal metabolism.

The diagnosis of Graves' disease is simple when the cardinal signs are present. Clinically, however, one meets patients in whom one or the other of these signs is absent; for instance, one frequently sees patients with tremor, tachycardia and enlarged thyroid gland without exophthalmos (23.2 per cent, Sattler¹) and others with tremor, tachycardia and exophthalmos but without an enlargement of the thyroid. Nevertheless, clinicians have tacitly included such patients within the province of Graves' disease. Difficulty enters as to the strict nosologic status of the exceedingly common group of patients who present all the classic evidences of the neuropathy of Graves' disease but who show little of the physical evidences except perhaps a tachycardia and a tremor. These patients are sensitive, emotional, anxious, tense and irritable. These are the cases that have been diagnosed variously as *formes frustes*, autonomic imbalance (Hyman and Kessel²), "Basedowoid" (Stern³) and "pre-Basedow" (Zondek and Bansi⁴). During the World War, a certain proportion of the patients whose cases were diagnosed as "neurocirculatory asthenia" presented these phenomena. The matter is further complicated by the fact that the clinical picture of *formes frustes*, etc., is not sharply drawn. For instance, Freidlander and Freyhof⁵ reported that in 20 per cent of their cases of "neurocirculatory

* Submitted for publication, Feb. 24, 1930.

* Read before the Medical Section, Philadelphia Academy of Medicine, Nov. 25, 1929.

1. Sattler: *Die Basedowische Krankheit*, Leipzig, Wilhelm Engelmann, 1910.
2. Hyman, H. T., and Kessel, Leo: *Exophthalmic Goiter (Graves' Syndrome) and Involuntary Nervous System*, J. A. M. A. **85**:1017 (Oct. 3) 1925.

3. Stern: *Jahrb. f. Psychiat. u. Neurol.* **39**:180, 1909.

4. Zondek, H., and Bansi, H. W.: *Klin. Wchnschr.* **8**:1697, 1929.

5. Friedlander, Alfred, and Freyhof, W. L.: *Intensive Study of Fifty Cases of Neurocirculatory Asthenia*, *Arch. Int. Med.* **22**:693 (Dec.) 1918.

siderably lower than in the normal cases, and its occurrence was nearly without relation to the height of the sugar level. The greatest difference, 29 mg. per hundred cubic centimeters, found in case 1, occurred at the third hour; case 2 is the only one in which the maximal difference coincided with the peak of the curve. In cases 5 and 6, the arteriovenous differences were practically negligible, indicating a total lack of dextrose utilization in the peripheral muscles. Further studies are necessary to determine whether such patients are to be classified as totally diabetic, and whether the magnitude of the arteriovenous difference can furnish a better measure for the classification of diabetic patients than the simple blood sugar curves of venous or arterial blood alone.

SUMMARY

After ingestion of 100 Gm. of dextrose, the arteriovenous difference in blood sugar content showed such wide maximal variations (from 2 to 60 mg. per hundred cubic centimeters) that no normal standard could be predicated.

In a small number of diseased but nondiabetic persons studied, the maximal arteriovenous blood sugar differences (from 19 to 40 mg. per hundred cubic centimeters) were in the lower half of the range determined for normal persons.

In three of six patients with diabetes studied, the maximal arteriovenous blood sugar difference lay just within the lower limits of the normal range. In the other three, it was definitely reduced.

It would seem unjustified, on the basis of present knowledge, to attach a diagnostic significance to the arteriovenous difference in blood sugar content. It remains to be determined whether diabetic patients can be regrouped into two therapeutic or prognostic groups depending on whether the arteriovenous difference in blood sugar content lies within or below the range determined as normal.

which extended long before and projected long after the period of observation. To classify a malady on signs that are subject to change is entirely artificial and misleading. One might as well regard the tadpole as an animal different from the frog.

It is becoming increasingly apparent that in order to be able to classify diseases on a sound biologic basis, one must observe disease over a far greater period than one has been accustomed to think. There are probably many maladies regarded as distinct species, which are in reality merely stages of disease processes that have thus far received different names and the relation of which is still unsuspected. Such observations are obviously more within the scope of the practitioner than of those who work in institutions or as consultants.

I had the fortunate experience of having witnessed the development of classic Graves' disease in a number of patients whom I had known and observed many years before. In no instance were the patients normal. They were sensitive, sanguine, quick, restless, temperamental, overstimulated and emotionally unstable, with bright eyes, and they invariably had rapid pulses and slight tremors which increased in periods of mental strain or emotional crisis. Their bowels moved under even slight emotion. These people were unusually slender. In other words, they corresponded precisely to the formula described by others as *formes frustes*, autonomic imbalance, basedowoid or pre-basedow. Their basal metabolism is within the normal range, but usually veers toward the plus side. The transition to the true Graves' disease, which is fairly sudden and often dates from some psychic insult, is characterized by an exaggeration of the tremor and the tachycardia; with these come abnormal sweating, loss of weight and often gastro-intestinal disturbances, with diarrhea or vomiting; soon a thyroid swelling appears, and the last important sign to develop is exophthalmos and its other attendant ocular phenomena. The basal metabolism is usually well toward the plus side. The classic clinical picture of Graves' disease is then complete.

The most interesting story in the evolution of this disease comes if the patient responds to whatever treatment is prescribed. The basal metabolism decreases more rapidly when subtotal thyroidectomy is performed than after medical treatment, because the thyroid gland is responsible for 40 per cent of the bodily heat (Dubois¹²). The patient gains weight, the pulse rate drops and the tremor subsides. The last symptom to disappear is the exophthalmos; it often persists throughout life. However, that which never disappears is the personality of the patient. The patient is still sensitive, emotional, restless, temperamental, sanguine, etc. Indeed, in this sense, the patient with Graves' disease

12. Dubois: *Basal Metabolism in Health and Disease*, Philadelphia, 1927.

asthenia" there was thyroid swelling, and in 6 per cent exophthalmos, while Lewis⁶ found a swelling of the thyroid gland in 4 per cent. Brooks⁷ found thyroid swelling in two thirds of his cases of neurocirculatory asthenia, especially in those of long duration; in such instances, also, he found exophthalmos. Addis and Kerr⁸ found that patients with all the clinical evidences of neurocirculatory asthenia had an enlarged thyroid in about half the instances, although they believed that many of these enlarged thyroids were of an endemic origin. In civil life one sees the counterpart of this picture in the "neurotic" young woman whose pulse is consistently rapid and whose thyroid swells at every menses or during emotional stress and in "neurotic" men during periods of emotional crisis. Between this primitive type and the complete end-product, with the quadrad of cardinal symptoms, including the increased basal metabolism, one finds an almost endless variety of clinical combinations: tachycardia, tremor and enlarged thyroid without exophthalmos; tachycardia, tremor and exophthalmos without an enlarged thyroid; enlarged thyroid and elevated basal metabolism rate but without exophthalmos; increased basal metabolism without thyroid enlargement, etc.; but there is one common denominator in the vast majority of these combinations of clinical signs, the neuropathic personality already described. Despite the strong resemblance between this incomplete or aberrant picture and the finished product represented by the term Graves' disease, the majority of clinicians have been unwilling to regard the *formes frustes* as related to Graves' disease, and the reasons therefore are various. Carroll⁹ held that some types of neurocirculatory asthenia and hyperthyroidism are identical. Barr¹⁰ regarded neurocirculatory asthenia as a form of Graves' disease. Nevertheless, Grant,¹¹ in a five year follow-up of neurocirculatory asthenia, found that none of the patients had developed the fully fledged form of Graves' disease.

The issue of classification depends, as in so many provinces in medicine, on the interpretation of disease from the biologic rather than from the static point of view. In analyzing the opinions on this matter, one deduction becomes clear, namely, that most physicians regard the disease at the time of observation, as having reached its fullest development and not merely as one phase of a process the natural history of

6. Lewis, Thomas: *Soldier's Heart and the Effort Syndrome*, New York, Paul B. Hoeber, Inc., 1919.

7. Brooks, H.: *Am. J. M. Sc.* **156**:726, 1918.

8. Addis, Thomas, and Kerr, W. J.: *The Relative Frequency in Recruits With and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia*, *Arch. Int. Med.* **23**:316 (March) 1919.

9. Carroll, J. H.: *Am. J. M. Sc.* **158**:35, 1919.

10. Barr, J.: *Brit. M. J.* **1**:544, 1916.

11. Grant, R. T.: *Heart* **12**:121, 1925-1926.

in general terms as the sensitive emotional type, and furthermore, that no matter what kind of treatment is instituted, his personality persists although all other evidences of the disease have been eliminated. There is no physical make-up that is characteristic of the disease, for it occurs in persons of every variety of build. These people are touchy and extraordinarily sensitive to their environment. A look, a harsh word or a hostile attitude will upset them deeply and often irrevocably. As a consequence they are usually intolerant. They blush, sweat and become pale easily. In consequence of this unusual sensitiveness, they are apt to be shy and introverted. They are extraordinarily unstable in their emotivity, so that their moments of ecstasy and depression are widely removed. The curve of their mental life has wider excursions than that of the phlegmatic person, which is comparatively flat. They are quick and hasty in their movements and thoughts and are frequently irascible. They are sanguine and temperamental. They are prolific day dreamers, and ideation plays a large rôle in their mental life. Many of those who are described as having the "artistic" temperament belong to this group of persons. They are especially sensitive to thyroid preparations, while their opposites, the phlegmatic type, usually are not. They are usually bad sleepers. An exceedingly common observation is the history of "nervous" diarrhea following any emotional upset, such as a school examination, untoward news or a fright. Also, under such circumstances, the pulse quickens and there is trembling. Their powers of concentration are limited, and they become tired easily, both mentally and physically.

This type of person, in his main essentials, has been recognized ever since Charcot¹³ gave an excellent description, but it is only in recent years that its relation to constitution has been recognized. Kocher¹⁴ and Chvostek¹⁵ summarized the type as belonging to the sanguine temperament. Oswald described this type as especially sensitive to thyroid medication, iodine and roentgenization of the thyroid, and as the frequent precursor of Graves' disease. Stern,³ who invented the term "basedowoid," while appreciating the similarity to Graves' disease, nevertheless differentiated "basedowoid" from the latter on such artificial grounds as the greater severity and the more acute onset of Graves' disease. Bauer¹⁶ was probably the first to place this predisposing type of person formally within the category of the constitutional diseases.

13. Charcot, quoted by Chvostek: *Morbus Basedow und die Hyperthyrosen*, Berlin, 1917.

14. Kocher: *Arch. f. klin. Chir.* **92**:677, 1910.

15. Chvostek: *Morbus Basedow und die Hyperthyrosen*, Berlin, Julius Springer, 1917.

16. Bauer: *Die konstitutionelle Disposition zu inneren Krankheiten*, Berlin, Julius Springer, 1921.

is never completely cured, although he may be socially and economically restored. In fact, even in this condition, the patient is liable to greater or lesser recurrences of the disease, subject largely to his environmental adjustment. The other sequelae of Graves' disease are various and need not be discussed fully. Death from thyrotoxicosis, so called, is rare, and may occur at its inception or after any recurrence. Other persons become frank cardiac patients, as the result of the development of various arrhythmias (usually auricular fibrillation), cardiac hypertrophy from the persistent tachycardia and consequent increased volume output or the development of hypertension and its consequent cardiovascular phenomena. Death from cardiac insufficiency is late, often twenty years after the onset of the first signs of Graves' disease. I have witnessed a number of instances of the development of cardiac disease in patients who never passed beyond the stages of *formes frustes*. Once cardiac disease has developed, it is extremely difficult to cure by any of the recognized methods of therapy, but in a number of instances I have seen auricular fibrillation disappear after a subtotal thyroidectomy.

The point that I wish to make is that Graves' disease has a natural history, that its beginnings long antedate the full-blown clinical form, that its evolution is various and that in order to interpret this evolution, observations extending over many years, often throughout the life-time of the afflicted person, are necessary. It is incumbent on physicians, therefore, to be far more elastic in evaluating the criteria of diagnosis than they have been in the past; as shall be seen, it is rather in the summation of the various disease processes than in the rigid establishment of one or more criteria that the diagnosis is rendered possible. Certain of these criteria will be discussed later. It is for this reason that the term "syndrome" is more applicable in this connection than the term "disease," and so I shall call it henceforth.

Graves' syndrome, however, is not merely a combination of signs and symptoms. The study of this disease has convinced me that there is a common denominator, namely, the personality I have already described, which has been termed *formes frustes*, "basedowoid" and autonomic imbalance. There is no doubt in my mind that this personality is not the result of the disease, as some aver. In terms of modern usage, this personality may be termed part of the constitution of the disorder, although how far this personality is the result of environmental or of anatomic factors still requires extensive study.

THE CONSTITUTIONAL FACTOR IN GRAVES' SYNDROME

I have tried to show that if the patient is studied before the onset of the Graves' syndrome or if his personality is reconstructed afterward, he will conform to a class of individuals that may be described

and high-strung; many have passed through "nervous breakdowns"; anxiety neuroses, hypochondriasis and psychasthenias are common; even true hysteria and psychoses are encountered.

This familial constitutional tendency has been noted frequently before. Charcot¹³ first called attention to this neuropathic tendency. Numerous similar observations are reported in Sattler's monograph, in Bauer's monumental work on the "Constitution" and by Ostwald,²⁴ Pässler,²⁵ Holst,²⁶ Barker,²⁷ Falta,²¹ Biedl²⁸ and Buschan.¹⁸

The observations on patients with neurocirculatory asthenia frequently bring to light a family history of a neuropathic tendency (Robey and Boas,²⁹ Oppenheimer and Rothschild,³⁰ Brooks,⁷ Neuhof³¹). Lenz expressed the belief that this tendency is transmitted according to the Mendelian law. This constitution becomes apparent at a very early age, usually just at or before the period of puberty.

There is no doubt in my mind that this constitution is a familial trait. Is it congenital and hereditary in the sense that a gene is transmitted or is it acquired? Holst²⁶ expressed the belief that it is congenital, in the sense that there is a disturbance in the anlage of the nervous and the endocrine system. Warthin,¹⁷ who said that the thymicolymphatic anatomic basis is the potential of this constitution, naturally believes it a congenital trait.

I believe that in the light of the modern study of the effect of environment on psychologic characteristics, it would be rash to jump too quickly to the conclusion that because a disease is familial and even hereditary it is congenital and transmissible. Here one is again confronted with the ancient controversy among biologists as to whether or not acquired characteristics, of which the constitution mostly consists, are transmissible. Certainly the burden of proof thus far rests with those who say that they are. Admitting, however, that part of the constitution is congenital, as in Warthin's sense, there is no doubt that the psychologic aspects in this constitution are affected profoundly by

24. Ostwald: München. med. Wchnschr. **27**:907, 1915.

25. Pässler: Deutsche Ztschr. f. Nervenhe. **6**:210, 1895.

26. Holst: Acta chir. Scandinav., 1923-1924, suppl. 4.

27. Barker, L. F.: Nervous and Mental Symptoms in Exophthalmic Goiter, J. A. M. A. **71**:327 (Aug. 3) 1918.

28. Biedl: The Internal Secretory Organs, New York, William Wood & Company, 1913.

29. Robey, W. H., and Boas, E. P.: Neurocirculatory Asthenia, J. A. M. A. **71**:525 (Aug. 17) 1918.

30. Oppenheimer, B. S., and Rothschild, M. A.: The Psychoneurotic Factor in the Irritable Heart of Soldiers, J. A. M. A. **70**:1919 (June 22) 1918.

31. Neuhof, S.: The Irritable Heart in General Practice, Arch. Int. Med. **24**:51 (July) 1919.

He acknowledged that under certain noxa (fear, infections, etc.) persons with such constitutions may develop Graves' disease, and brought in the vegetative nervous system, in which the thyroid is inserted as a "multiplicator" to explain most of the phenomena. Warthin¹⁷ described this constitution perfectly, but, accepting the anatomic interpretation, he expressed the belief that this constitution has a constant anatomic substratum, namely, a thymicolymphatic hyperplasia, evidences of which are seen in the constant presence of hyperplastic lymph nodules in the thyroid, the presence of an enlarged thymus, etc.

Admitting, as all evidence seems to show, that a constitutional factor forms the background of Graves' disease, the matter is by no means settled by merely giving a label. The word constitution has a wide connotation, especially in respect to how far the elements forming such a constitution are congenital, hereditary or acquired.

RELATION OF GRAVES' SYNDROME TO HEREDITY

In Graves' syndrome the family history is highly illuminating. Most clinicians with considerable experience in Graves' syndrome have noted its occasional occurrence in two or more members of the same family. I have seen a number of such instances. Sattler,¹ in his exhaustive monograph, reported many. Buschan,¹⁸ Lerrede and Drouet,¹⁹ Moss,²⁰ Bauer,¹⁶ Chvostek,¹⁵ Falta²¹ and numerous others reported instances. Souques and Lermoyez²² reported seven cases of Graves' syndrome in sixteen adults of one family covering three generations. This familial tendency is so common that it may be considered as occurring more frequently than the mere laws of chance would determine. Less frequently, Graves' disease has been reported as occurring in mother and child (Sattler¹), Bauer,¹⁶ Lenz.²³

Of far greater import than the exposure of a familial or a hereditary tendency of the full-fledged Graves' syndrome is the revelation that the study of the relatives of the patients with this disease affords in appreciating the constitutional factor. In the instances in which I have had the opportunity to study such families, I have invariably found that the immediate relatives are what has been poorly termed "neurotic." They possess many or all of the characteristics that have been described as belonging to the constitutional type. They are "nervous," sensitive

17. Warthin: *Ann. Int. Med.* **2**:553, 1928.

18. Buschan: *Die Basedowische Krankheit*, Leipzig and Vienna, 1894.

19. Lerrede and Drouet: *Bull. Soc. franç. de dermat. et syph.* **28**:142, 1921.

20. Moss: *New York M. J.* **99**:482, 1914.

21. Falta: *Handbuch der inneren Medizin*, 1927, vol. 4, second part

22. Souques, A., and Lermoyez, J.: *Rev. neurol.* **35**:20, 1919.

23. Lenz: *Arch. f. Rassen- u. Gesellsch.-Biol.* **13**:1, 1918.

elucidate the relation of Graves' syndrome to enlargement of the thymus gland, it is not necessary to theorize on any mutual activity of one organ on the other. It is sufficient merely to bring the characteristics of patients with the thymus constitution into harmony with the characteristics of patients with Graves' syndrome. This is a matter of observation entirely. It is well known that persons with the thymic constitution are extraordinarily sensitive, not only to physical influences such as traumatism, narcosis, infections, etc., but also to psychic influences. The latter is proved by the frequency of suicides and of neuroses among such patients (Kolisko,³⁴ Parataschew³⁵). As the essential characteristic of the constitution of Graves' syndrome is the extraordinary sensitivity to physical and psychic stimuli, is it not reasonable to assume that the thymic constitution is merely a potential basis, not necessarily universal, for the development of Graves' syndrome? There are a number of facts that tend to harmonize both conditions: 1. As with Graves' syndrome, the persistent thymus is frequently a familial and hereditary condition. 2. The lymphocytosis, present in from 80 to 90 per cent of cases of Graves' syndrome and now regarded as evidence of the status thymicolymphaticus, does not disappear after thyroidectomy or after any form of treatment. The observation of Storck,³⁶ who found a lymphocytosis in the families of patients with Graves' syndrome, suggests a basic familial constitution as the background for the incidence of the disease, the lymphocytosis being entirely independent of thyroid influences. 3. Lymphoid hyperplasias are found with extraordinary frequency in thyroids removed from patients with Graves' syndrome. That these lymphoid deposits are not the result of inflammatory or other changes consequent on Graves' syndrome is shown by their presence in the vast majority of cases of status thymicolymphaticus, whether associated with the syndrome or not (Warthin,³⁷ Simmonds³⁷). Hecker³⁸ also found such lymphatic deposits in 12 per cent of normal thyroid glands. There is evidence, therefore, that these areas of lymphatic tissue precede the incidence of Graves' syndrome and represent part of the thymicolymphatic constitution. Warthin,³⁷ in a publication revealing fine penetrating insight, regarded these deposits as more constant and of far greater import than the epithelial hyperplasia, and expressed the opinion that they represent the only real anatomic constitution of Graves' syndrome. Unquestionably the thymicolymphatic constitution represents the constitution in the vast

34. Kolisko: *Lehrbuch der gerichtliche Medizin*, Berlin and Vienna, 1902.

35. Parataschew: *Virchows Arch. f. path. Anat.* **273**:134, 1929.

36. Storck: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **10**:417, 1914.

37. Simmonds: *Virchows Arch. f. path. Anat.* **211**:73, 1913.

38. Hecker: *Frankfurt. Ztschr. f. Path.* **28**:96, 1922.

environmental factors, in most instances by the influence of parents on children. In two instances of families in which Graves' syndrome occurred, the neuropathic constitution was directly traceable to a high-strung, sensitive, intolerant and extremely ambitious mother. In another, it was the result of a fussy mother with an anxiety neurosis, who so petted and shielded her brood in infancy and childhood that when the children reached the age of discretion they were unable to cope with the ordinary tribulations of everyday life.

THE RELATION OF THE THYMUS TO GRAVES' SYNDROME

Warthin's observations bring up the important relation between the thymus and Graves' syndrome. The frequent association of Graves' disease and enlarged thymus has been emphasized repeatedly. According to Seelig,³² an enlarged thymus is found in from about 80 to 90 per cent of fatal cases of Graves' disease, while Haberer found a large thymus in 100 per cent of those dying from operation. Kocher¹⁴ found an enlarged thymus in about 50 per cent, and Hammer³³ in about 63 per cent of all patients with Graves' syndrome. In Mount Sinai Hospital, New York, a large thymus was found in 95 per cent of fatal cases of Graves' syndrome. The enormous incidence of the thymicolymphatic constitution in this syndrome means something, and calls for an answer to the following questions: 1. How far does the thyroid affect the thymus? 2. How far does the thymus affect the thyroid gland? 3. Is there a relationship between these organs, and are their diseases therefore the simultaneous reactions to the same insult? 4. Is it possible for the thymus gland to undergo involution and then regenerate? 5. Are the lymphatic infiltrations within the thyroid gland so commonly present in Graves' syndrome evidences of a thymicolymphatic constitution or are they the result of some other factor, for instance, inflammation? Some of these questions can be answered quickly. That the thymus does not activate the thyroid gland in Graves' syndrome is shown by the fact that an enlarged thymus is exceedingly common without Graves' syndrome and that the lymphocytosis, which all agree is a symptom of the thymic constitution, persists after thyroidectomy (Chvostek¹⁵). That the thyroid gland does not necessarily cause hyperplasia of the thymus is shown by the fact that Graves' syndrome is common without any evidence of thymic enlargement.

That Graves' syndrome and thymic enlargement are not simultaneous reactions to the same insult is shown by the frequency with which they are totally dissociated in the same patient. In order to

32. Seelig: *Interstate M. J.* **20**:678, 1913.

33. Hammer: *Folia neuro-biol.* **12**:209, 1922.

The genesis of what may be called an attack of a mild form of Graves' syndrome is seen on a larger and more extensive scale in the development of a florid Graves' syndrome as the result of mental shocks of greater intensity. Every clinician is struck by the common clinical story that the onset of Graves' disease occurred promptly after a psychic insult or an intense emotional crisis. I have seen it occur after a robbery, a fire, a pogrom, a frightful sexual experience, a terrible confinement, an unwelcome pregnancy, the death of a close relative, the desperate illness of a child, an unrequited maternal affection, a sudden loss of possessions, the dread of an operation, an automobile accident, failure in a college examination, a hateful engagement forced on the daughter by the parents and the sudden onset of deafness.

It is notorious that there was a sudden crop of cases of Graves' syndrome in Vienna after the theater fire horror in 1882 and after the San Francisco earthquake. McCarrison⁴² reported the interesting observation that in India, where endemic goiter is common, Graves' syndrome was exceedingly rare before the World War (probably because of the phlegmatic character of the natives engendered by their religions), while after the war, when the Indian soldiers returned, this disease became exceedingly common. Testimony is abundant, just as with neurocirculatory asthenia, from Marañon,⁴³ Étienne and Richard,⁴¹ Merklen,⁴⁰ Railliet,⁴⁴ Kahane,⁴⁵ Rothackers,⁴⁶ Johnson,⁴⁷ Bär⁴⁸ and Dannehl,³⁹ that an enormous number of cases of Graves' syndrome arose as the result of fear during the World War.

It is unnecessary to quote the testimony of the host of observers who have noted the direct relation of fear to the onset of Graves' syndrome. Crile's⁴⁹ observations are especially interesting, not only because of his emphasis on fear as the inciting agent, but because of his plausible thesis that the characteristic facies and most of the symptoms of the patient with Graves' syndrome and those in man or in an animal in a state of fear are remarkably alike, and that fear is a phylogenetic attempt at flight or escape. Furthermore, realizing the important element of fear in the psychology of patients with this disease, he devised a most practical and worthy system of preoperative care in which the fear of the operation was reduced to a minimum.

42. McCarrison, Robert: *Proc. New York Path. Soc.* **21**:154, 1921.

43. Marañon, G.: *Ann. de méd.* **9**:81, 1921.

44. Railliet: *Bull. et mém. Soc. méd. d. hôp. de Paris* **42**:1151, 1918.

45. Kahane: *Wien. klin. Wchnschr.* **28**:148, 1915.

46. Rothackers: *München. med. Wchnschr.* **63**:99, 1916.

47. Johnson: *Lancet* **2**:920, 1916.

48. Bär: *Klin. Monatschr. f. Augenh.* **59**:105, 1917.

49. Crile: *Am. J. M. Sc.* **145**:28, 1913.

majority of cases of Graves' syndrome, but it cannot be the only one, because it has been repeatedly demonstrated that Graves' disease can occur in the absence of any evidence of the thymicolymphatic constitution. It is more consistent with established facts to assume that the basic constitution of Graves' syndrome is an entity characterized by an extraordinary sensitiveness to physical and mental influences, that in the majority of cases this sensitiveness is determined by certain anatomic peculiarities, and that in the remaining cases it is determined by environmental influences. Why a person afflicted with the thymicolymphatic constitution should show a heightened sensitivity to both physical and mental stimuli, I do not know.

The apparently inconsistent anatomic relations between the thyroid and the thymus gland and the belief that the disease was primarily glandular in origin led many investigators to the conclusion that the etiology of Graves' disease was threefold—thymogenic, thyrogenic and thyrothymogenic. Many surgeons advocated removal of the thymus gland in patients in whom thyroidectomy proved inadequate. In the light of what has already been set forth, one can readily grasp the fallacy of these conclusions, and, indeed, thymectomy for the cure of Graves' disease is now a matter only of historical interest.

Even if one admits that the neuropathic constitution is the potential of Graves' syndrome, it still remains to be explained why only a small proportion of patients with such constitutions develop the disease while others do not. There must be another factor, and this I maintain is again psychic.

EXCITING CAUSE OF GRAVES' SYNDROME

I have already called attention to the fact that when patients with the aforementioned constitution are observed shortly after periods of mental stress and emotional strain, they develop palpitation with tachycardia and trembling, and in protracted crises, even a slight swelling of the thyroid; sometimes even the eyes become more prominent. In most instances, these evidences subside when the patient calms down. Most of the observers who report on the cause of neurocirculatory asthenia during the World War, while admitting the constitutional and familial background, regard fear or emotional strain as the exciting factor (Dannehl,³⁹ Merklen,⁴⁰ Étienne and Richard,⁴¹ Brooks,⁷ Robey and Boas,²⁹ Carroll⁹). In the neurocirculatory asthenia of civil life, I have frequently noted exacerbations due to fear. Neuhof³¹ reported similar observations.

39. Dannehl: *Deutsche mil.-ärztl. Ztschr.* **44**:44, 1915.

40. Merklen: *Bull. et mém. Soc. méd. d. hôp. de Paris* **41**:894, 1917.

41. Étienne and Richard: *Bull. et mém. Soc. méd. d. hôp. de Paris* **42**:1196, 1918.

Graves' syndrome, such as tachycardia, tremor, some thyroid swelling and elevation of the basal metabolic rate. It is rare for exophthalmos to develop. The symptoms usually subside promptly with the withdrawal of the drug. In the phlegmatic person, it is rare to see any profound effect even after comparatively large doses.

The effects of the administration of thyroid gland to susceptible people, the almost constant association of thyroid swelling and Graves' syndrome, the alleviating effects of removal of large portions of this gland, the clinical opposition between Graves' disease and the acknowledged hypothyroidism of myxedema and, finally, the histologic evidences of epithelial hyperplasia in the vast majority of thyroid glands removed in cases of Graves' syndrome have led to the conception, prevalent since Möbius, that hyperthyroidism represents a large component of Graves' syndrome. There is no doubt that all of the evidence points that way. I do not imply that hyperthyroidism is the equivalent of Graves' syndrome. To me this syndrome represents hyperthyroidism plus constitution and perhaps other unknown factors. The problem remains, however, whether the thyroid is the primary origin of the disease and the psychic and other manifestations secondary, as many aver, or whether the thyroid manifestations are secondary and the results of other causes.

There are many reasons why the thyroid gland cannot be regarded as the primary origin of the disease. 1. It is well established that hyperthyroidism is not more common in districts where endemic goiter is prevalent, e. g., around the Great Lakes of the United States, in Switzerland and in India (McCarrison)⁵⁴. McCarrison stated that before the World War, Graves' syndrome was extremely rare in goitrous districts, and was present only among the European residents. I shall not enter largely into the problem as to whether the distinction made by Plummer between Graves' syndrome and adenoma with hyperthyroidism is valid or not. As far as I can judge, these two diseases are the same, differing only in intensity. The same constitutions underlie both; the anatomic characters are the same, the results of thyroidectomy are alike, and the main exciting agent, fear, is a dominant factor in both conditions. Modern opinion is largely veering in this direction. 2. In clinically well recognized cases of Graves' syndrome the thyroid is often not only absent, but in about from 10 to 15 per cent no evidence of hyperplasia is present (Holzweissig,⁵⁵ Simmonds,³⁷ Klose and Hellwig⁵⁶). Warthin would exclude such instances from Graves' syndrome, but this is hardly justifiable, because it would validate the argu-

54. McCarrison, Robert: *The Thyroid Gland in Health and Disease*, New York, William Wood & Company, 1917.

55. Holzweissig, H.: *Deutsche Ztschr. f. Chir.* **193**:276, 1925.

56. Klose, H., and Hellwig, A.: *Arch. f. klin. Chir.* **128**:175, 1924.

In some instances (I should estimate one-fifth), a history of fear or a sudden emotional crisis cannot be obtained. Such a failure may be due to reticence on the part of the patient or my inadequacy as a psychologist in the approach to the patient. In a few instances, a trained analyst has succeeded in obtaining such a history when I have failed. In others, however, even an exhaustive questioning has failed. In a few of these, I have obtained the impression that the Graves' syndrome arose imperceptibly from the constitutional state, i. e., *formes frustes*, etc., as the result of the cumulative effect of repeated mental strains of lesser degree. I witnessed one such instance in a woman who married late, and who practiced extraordinary sexual abuse.

In the residuum of 20 per cent in which a history of fear cannot be elicited, a large number give a history of the onset or reappearance of Graves' syndrome as occurring after an illness, usually an infection of the throat. This cause is also cited by observers as common. I am not entirely clear yet as to whether the actual infection is the inciting cause or the fear that the illness engenders. On deeper questioning, I have obtained the admission that during the illness there was fear of permanent invalidism or death. The illness may have been nothing more than tonsillitis, but to the sensitive victim any illness may appear serious. Fear is undoubtedly the basis of most of the many factors that have been cited as the cause of Graves' syndrome, such as pregnancy, confinement, the onset or cessation of menstruation, etc. For example, I recall instances in which Graves' syndrome was relieved by a much desired pregnancy, and one in which the syndrome, arising during pregnancy, was relieved after an easy confinement. Sattler¹ also mentioned such instances. That is why no hard and fast advice can be given to women with this constitution or with this syndrome in the matter of child-bearing. It should depend largely on their personal equation and adjustability.

In any event, the history of mental trauma is so common in Graves' syndrome that many, among whom may be mentioned Freud,⁵⁰ Stekel,⁵¹ Oppenheim⁵² and Pulay,⁵³ regard Graves' syndrome as a traumatic and anxiety neurosis.

RELATION OF THE THYROID GLAND TO GRAVES' SYNDROME

The administration of thyroid gland and thyroxin is poorly tolerated by patients with the Graves' constitution, because it intensifies most of the clinical manifestations with the development of mild forms of

50. Freud, quoted by Marcuse: *Deutsche med. Wchnschr.* **43**:70, 1917.

51. Stekel, quoted by Marcuse: *Deutsche med. Wchnschr.* **43**:70, 1917.

52. Oppenheim: *Lehrbuch der Nervenkrankheiten*, Berlin, S. Karger, 1923.

53. Pulay: *Ztschr. f. klin. Med.* **88**:87, 1919.

Graves' syndrome is rare in India among the native population (McCarrison). Sattler found that it is also rare among the Japanese and the colored races. Up to a decade or more ago Graves' disease was considered rare in the American colored population, but as I have had the opportunity to observe, it apparently is now on the increase, probably due to the sensitization acquired through close contact with civilization among the whites and industrialization.

Graves' syndrome is very common among the Jews (Fishberg), who are notoriously a highly sensitive and emotional people, consequent to the development of keen protective mechanism engendered by generations of persecution and defensive wanderings. Marcuse⁶¹ quoted Grotjean, who found Graves' syndrome more common in cities than in rural districts. This is as one would expect, for the strains of existence and the opportunity for psychic insult are greater in large centers of population. The incidence of Graves' disease is highest in the most civilized races and countries. This difference in incidence among races and countries depends on many other factors: the religion (whether it teaches resignation or irreconcilability in the face of vicissitudes), the social code, the character of the government, the suitability of the land for sustenance, etc. In general, those influences that tend toward conflict and the sensitization of the individual will breed Graves' syndrome. In the final analysis, therefore, Graves' syndrome is a social disease and is a product of the higher civilizations.

The Relation of Graves' Syndrome to Age.—This disease is rare before the age of puberty. In Hill's⁶² series of 206 cases, only 1 occurred before that age. Of the 3,447 cases collected by Sattler, only 184 were in children below the age of 15. Hill and others expressed the belief that the common incidence of Graves' syndrome at the time of puberty corresponds to the development of the sex instinct, and there is no doubt that at this time, in girls especially, the onset of the menses is attended by considerable mental strain. But to my mind, this is not so much the reason as the fact that at this age the reasoning and emotive powers become more subtle and adjustments become more sensitive. The constitution which has hitherto been potential is now developed.

DIAGNOSIS OF GRAVES' SYNDROME

As can be gathered from all I have thus far set forth, there is no single sign or test that will make the diagnosis of this disease absolute. It can be made only by taking into consideration a host of factors. The touchstone for the diagnostic approach is the reconstruction of the patient's personality or, in other words, his constitution. Of lesser

61. Marcuse: *Deutsche med. Wchnschr.* **43**:70, 1917.

62. Hill, H. G.: *Quart. J. Med.* **22**:217, 1929.

ment that because the majority of thyroid glands in Graves' disease show hyperplasia no case is Graves' disease unless the gland shows hyperplasia. Indeed, definitely clinical Graves' syndrome is extremely common without any thyroid hyperplasia. 3. There appears to be no parallelism between the extent and intensity of the hyperplasia and the clinical expression of the disease.

One must conclude, therefore, that despite the fact that many of the signs of Graves' disease are apparently the effects of hyperthyroidism, the gland itself is not the primary cause, and the changes that occur in the gland are the resultant factors. As the constant constitutional basis and the common excitant, fear, are of psychologic origin, these changes are probably the results of influences in the nervous system. Corroboration of this view is shown in the demonstration that the thyroid secretion is profoundly influenced by stimulation of the superior laryngeal nerve (Katzenstein,⁵⁷ Exner,⁵⁸ Wiener,⁵⁹ Ascher and Flack⁶⁰). How far the signs of Graves' syndrome are the result of imbalance of the autonomic nervous system (Hyman and Kessel)² or of the peripheral or central neurons cannot, in the light of present knowledge, be determined. It is probable that the autonomic nervous system is responsible for a considerable part of the clinical expression of the disease.

The definite etiologic relationship of the psychopathic constitution and the excitant psychic insult to Graves' syndrome explains: (1) the enormous preponderance of Graves' syndrome in the female sex, (2) the rarity of this disease in childhood, i. e., before the age of puberty and (3) the comparative freedom from the syndrome of certain races, e. g., East Indians, Chinese and negroes.

Relation of Graves' Syndrome to Sex.—In Sattler's extensive statistics the proportion of females to males is 5.44 to 1. The sensitiveness and responsiveness to the environment and the more subtle emotivity of the female sex are probably in part the result of generations of protection that the male has imposed. It is not to be wondered at that the female is more sensitive to fear. In the male, I have noted that Graves' syndrome often affects those who have been single, or the favorite or spoiled child. These persons also reveal the sensitivity engendered by too great an application of protective mechanisms.

The Relation of Graves' Syndrome to Race.—There is ample testimony that Graves' syndrome is unusual in races of coarser mental fiber, in countries where the social order is simple and where the people are noted for their phlegmatic temperament. Testimony is ample that

57. Katzenstein: Arch. f. Laryngol. u. Rhinol. **5**:285, 1896.

58. Exner: Arch. f. d. ges. Physiol. **68**:100, 1897.

59. Wiener: Arch. f. exper. Path. u. Pharmacol. **61**:297, 1909.

60. Ascher and Flack: Ztschr. f. Biol. **55**:83, 1910.

THE BEARING OF THE CONSTITUTION ON TREATMENT AND
RECURRENCES OF GRAVES' SYNDROME

If the relation of the constitution (autonomic imbalance, formes frustes) to Graves' syndrome is recognized, and, especially, if the fact that this constitution, whether determined by a status thymico-lymphaticus or environment, is an irradicable part and parcel of the patient's personality is recognized, and, furthermore, if one acknowledges that this constitution has the potentiality to flare up under the stress of a psychic insult, one can readily understand the vicissitudes that the various methods of treatment for Graves' disease have undergone. The therapy for no disease has covered so wide a range and has undergone such rapid changes as that for Graves' syndrome. It is best to "cast the poppy of oblivion" over the host of drugs and other methods that have been tried and found wanting. I shall not enter into the modern methods of therapy, except to say that no treatment which does not take into consideration the constitution and the exciting psychic insult can be completely effective. And this is where the great difficulty enters. For, as I have shown, a study of the individual constitution involves the study not only of the personality of the patient, but of his family, his environment, his social and economic status and, above all, his mental malleability. As far as the present outlook permits one to say, each patient requires not only discerning social service, but psychotherapy. Unfortunately, social service is not yet sufficiently adequate, nor is psychotherapy whether by freudian psychoanalysis or by character building, hypnotism, behaviorism or "skilful neglect," always capable of controlling some of the environmental factors. All these psychotherapeutic methods have brought about improvement and even "cures" (more or less temporary, rarely permanent), but the number of unsuccessful cases is still large.

The estimation of the different factors that enter into the constitutional make-up is decisive in regard to whether the patient should continue with psychotherapy or should resort to surgical intervention. If the environment can be controlled, if the constitutional defect is not too deeply seated within the patient, if the Graves' syndrome is not too florid and, above all, if the patient is mentally young enough to be psychically impressionable, psychotherapy is permissible. If one cannot get at the cause, one must get at the effect, and so one comes to surgical intervention. Although the cause of appendicitis is not known "cure" can be obtained by removal of the offending organ.

Surgical intervention for Graves' syndrome is obviously based on the gross evidences of hyperthyroidism. Here the treatment has been one of rapidly changing methods, varying from ligation of the thyroid arteries to partial excision and now to almost complete excision of the

importance, but nevertheless illuminating, is the determination of the exciting psychic insult. The insult is sometimes lacking, but as far as my experience goes, the constitution never is.

The custom has become prevalent in this country to regard the determination of the basal metabolism as the main diagnostic criterion of Graves' syndrome, especially in the differentiation of *formes frustes*, autonomic imbalance, etc., from the fully developed disease. For statistical purposes and as a means of offering some notion of the severity of the disease, a differentiation on the basis of a normal or heightened basal metabolism may be justified, but on a strict biologic basis such a differentiation cannot be regarded as anything but artificial. One can readily understand why this must be so when one considers that with the elevation of the basal metabolic rate, as with the elevation of a patient's temperature, there is no precise level that must be considered critical. Indeed, the basal metabolism determination in Graves' syndrome cannot be regarded of greater diagnostic value than that of clinical thermometry in febrile conditions, and the relation of Graves' syndrome to the *formes frustes* stage may be compared to that of the febrile and the nonfebrile period of an infectious disease. The best proof of the limitation of the basal metabolism as a diagnostic criterion of Graves' syndrome is the fact that all physicians observe cases of classic Graves' syndrome (so-called "spent" cases) without an increased basal metabolism. There is hardly any question that the basal metabolism had been elevated, but in the diagnosis one can be concerned only with data obtained at the time of observation. When the basal metabolism returns to the normal limit after thyroidectomy for Graves' syndrome, does one at the same time suddenly change the diagnosis? Most assuredly not. The basal metabolism may best be regarded not as a diagnostic sign of Graves' syndrome but as the sign of hyperthyroidism and as the best measure of activity of the disease that one possesses at present.

Others besides Warthin do not regard the clinical diagnosis of Graves' syndrome as proved unless the thyroid gland reveals the characteristic epithelial hyperplasia. Aside from the fact that, as has been shown repeatedly, no such hyperplasia has been demonstrable in certain cases of clinically classic Graves' syndrome, it is unreasonable to hold to a precise anatomic criterion when all evidence, as even Warthin admitted, shows that the pathologic thyroid is secondary and is merely a link in the chain of circumstances. It would be equally logical to say that a patient has not hypertension because anatomically the usual arteriosclerosis and nephritis were not present at autopsy, or that those diabetic patients in whom (as occasionally happens) the islands of Langerhans are found normal, did not have the disease.

2. The common denominator in all of these various stages is a characteristic temperament or personality which may best be termed the sensitive and emotional type. In most instances this personality precedes the onset of the syndrome and persists even after all its grosser evidences have disappeared. This sensitive and emotional personality is a large element in the constitution which predisposes to the disease.

3. This constitution is often familial and hereditary. This is evident not only in the common history of "basedowoid," autonomic imbalance, formes frustes, etc., occurring in the same family, but in the fully developed Graves' syndrome as well. A study of the family history in this disease is therefore important and illuminating. In how far this constitution is hereditary or acquired cannot be judged, but there is no doubt that it is strongly influenced by environmental factors.

4. The thymicolymphatic constitution, when it co-exists with Graves' syndrome, represents the anatomic background on which this disease is engrafted. Persons with such constitutions are sensitive not only to physical, but to psychic insult, and possess the same familial and hereditary attributes as patients with Graves' syndrome. There is no evidence that the thymus gland activates the thyroid gland or vice versa.

5. The exciting cause of the fully fledged Graves' syndrome is usually traceable to a psychic insult which is in the nature of a surprise. Such an insult ushers in the transition between the primitive stage, i. e., formes frustes, etc., and the florid form of the syndrome. In most instances the essential ingredient in this insult is fear.

6. There is every evidence that excess of thyroid function represents the predominant evidences of Graves' syndrome. All evidence, however, shows that the hyperthyroidism is secondary and not primary. The characteristic hyperplasia of the thyroid gland in Graves' syndrome is therefore sometimes lacking.

7. The greater preponderance of Graves' syndrome in the female sex is the result of the greater sensitivity of the psyche in the female.

8. The racial incidence of Graves' syndrome conforms to what one would expect of ethnologic sensitivity. It is uncommon in races of coarser mental fiber and is common in those of subtler mental reactions and where the strain of existence is keener. Graves syndrome is apparently a social disease of the higher civilizations. In the development of the influences in which the disorder is likely to develop, religion, the social and political status, the availability of the country for sustenance, etc., are probably important.

9. The relation of the psyche to the development of Graves' syndrome is shown in the rarity of this disease in children, in whom the adjustable, reasoning and emotive powers are not fully developed.

thyroid gland. There is no doubt that the results of subtotal thyroidectomy are speedier and more lasting than those obtained by strictly medical means, but one must understand that all that surgical intervention has done is to depress rapidly the basal metabolism, for the thyroid gland is responsible for 40 per cent of the bodily heat. It acts like a prolonged antipyretic in a fever. A lowered bodily metabolism must be profoundly beneficial. It is intriguing to think that part of the good results of the operation may be due to the psychic effects of the operation itself. Crile ⁴⁹ discussed this aspect seriously, and concludes that psychology does not enter into the result.

Thyroidectomy, therefore, removes only the hyperthyroidism and the increase of basal metabolism; the personality of the constitution remains, a potential, given enough stimulus, to flare up into the more intense forms of Graves' syndrome. This accounts for the frequent and mysterious recurrences, no matter how thoroughly the operation was performed. As a rule, the recurrences are not usually of the severer variety of Graves' syndrome; the basal metabolism rarely reaches excessive figures, and the patients respond quickly to physical and mental rest and isolation from the environmental psychic insult. Furthermore, such recurrences may take place at any time, even years after the operation, so that reports of cures within a year or two after operation mean very little. Surgeons have been very remiss, therefore, in discharging their patients after operation without any regard to the environment to which they return; some, fortunately, realize this and give their patients instruction for the ensuing year or two. The lesson that these recurrences teach is that the treatment of the patient begins only after the operation has been performed.

SUMMARY

1. The classification of Graves' disease must be regarded from the dynamic rather than from the static point of view. In other words, it does not merely represent a disease in which various signs are artificially grouped together, but rather a biologic series of disorders that have received various names in the past. The natural history of the disease extends over a long period. The earliest phase is that heretofore known as *formes frustes*, "basedowoid," autonomic imbalance, etc.; the final stage is that conventionally termed Graves' disease, with the characteristic quadrad of signs—tremor, tachycardia, enlarged thyroid gland and exophthalmos. Between the primitive and the final florid form, one clinically finds various combinations of signs and symptoms. For this reason the name Graves' syndrome rather than Graves' disease is preferable.

THE OXYGEN AND CARBON DIOXIDE CONTENT OF BLOOD FROM THE INTERNAL JUGULAR AND OTHER VEINS*

WILLIAM G. LENNOX, M.D.

WITH THE ASSISTANCE OF ERNA LEONHARDT

BOSTON

A principal function of the blood is that of respiration, giving oxygen to the tissues and receiving carbon dioxide. The difference in the gaseous content of arterial and venous blood is a measure of the metabolic activity of the tissues or of the speed of the blood flow through them, or of both. To what extent do the various portions of the body vary in their utilization of oxygen? Is the blood taken from a superficial vein of the arm essentially the same in its gaseous composition as blood taken from other accessible veins?

The only observations bearing on this subject that we have seen are those made during certain experiments on animals by Uyeno and Dor.¹ They gave values for the oxygen saturation of the blood (as determined by the Barcroft differential apparatus) in various veins in six experiments. These values varied widely.

In order to answer the questions outlined for the human subject, we have measured the oxygen and carbon dioxide content of blood from various blood vessels, viz., the brachial, radial or femoral artery, the internal and external jugular, the femoral and the basilic veins.

METHODS AND MATERIAL

In order that the results should be as dependable as possible, certain precautions were observed. The subjects were required to lie quietly for half an hour before the blood was taken. This was drawn without the aid of a tourniquet, with the vein at the level of the heart. The room temperature was kept constant. Care was taken to avoid pain on puncture by preliminary local anesthetization of the skin. For puncturing the internal jugular vein we used the technic described by Myerson and his associates.² We first carefully anesthetized the tissues to be traversed by means of 1 or 2 cc. of a 1 per cent solution of procaine hydro-

* Submitted for publication, March 1, 1930.

* From the Department of Neuropathology of Harvard Medical School and the Thorndike Memorial Laboratory, Boston City Hospital.

1. Uyeno, K., and Dor, Y.: Studies on the Respiration and Circulation in the Cat: II. The Oxygen in the Venous Blood, *J. Physiol.* **57**:14 (Dec.) 1922.

2. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular and Internal Carotid Artery, *Arch. Neurol. & Psychiat.* **17**:807 (June) 1927.

10. The determination of the basal metabolism should not be regarded so much as a diagnostic sign of Graves' syndrome as a measure of the most prominent symptom, namely, hyperthyroidism, and therefore of activity.

11. If the relation of the constitution to Graves' syndrome is recognized, it will help to explain the many failures after treatment, whether medical or surgical. This constitution persists after any form of treatment, so that cure is never wholly obtainable. The most profound effect of thyroidectomy is on the basal metabolism. Furthermore, this constitution being profoundly influenced by environment, the treatment of the patient should not cease after thyroidectomy.

average results obtained in forty experiments are shown in table 1 and in the left hand portion of chart 2. In this larger group the composition of the arterial blood was more nearly normal than in the smaller group. (Many of the epileptic subjects used had a low oxygen saturation of the arterial blood, a matter that will be presented elsewhere.) The gaseous content of the external jugular blood bore about the same relation to that of the arterial blood as in the smaller group. The difference between blood from the internal jugular and

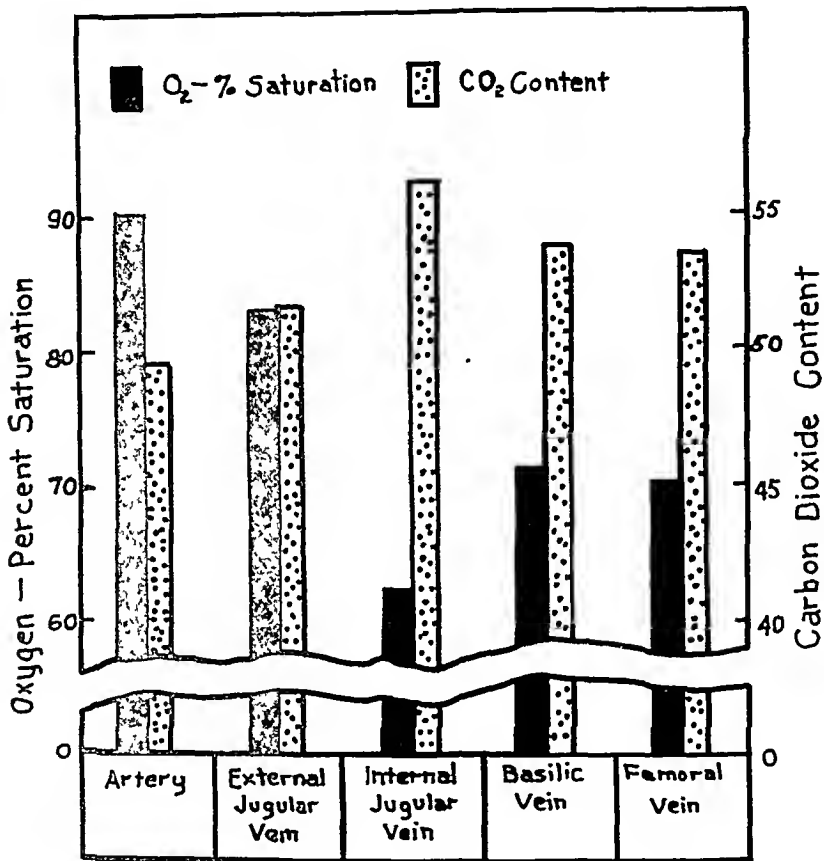


Chart 1.—Average results concerning the percentage saturation with oxygen (solid columns) and the carbon dioxide content (dotted columns) of the blood in fourteen patients, the blood being drawn from an artery and the external jugular, internal jugular, basilic and femoral veins. The percentage saturation with oxygen is given in the left hand ordinate and the carbon dioxide content in the right hand ordinate.

from the cubital veins was very nearly as great. In a still larger series of sixty observations, blood was obtained from only two veins, the internal jugular and a vein of the elbow. Here, as in the smaller groups, blood from the internal jugular vein was more nearly reduced than blood from a superficial vein of the arm. Results are shown in table 1 and in the right hand portion of chart 2.

chloride, introduced through a $1\frac{1}{2}$ inch 26 gage needle. For drawing the required 10 cc. of blood, a $1\frac{1}{2}$ inch 20 gage needle was used. If the patient did not remain relaxed or if he experienced undue pain, the attempt to obtain blood from the internal jugular vein was abandoned. It was not feasible to withdraw blood from the various loci simultaneously. Also it was thought that such a concerted attack would unnecessarily excite the subject, thus complicating the results. We therefore drew blood from the veins in sequence, varying the order in different patients. In some of the subjects used it was found that there was considerable variation in the gaseous content of blood drawn at intervals from the same vein. For this reason we believe that comparison of individual measurements is not of as much value as comparison of average values obtained from a fairly large group. Blood was taken under oil, and analysis was begun at once. The portable constant volume apparatus of Van Slyke³ was used.

None of the subjects had any serious cardiac or pulmonary lesion. All were patients in the neurologic service of the Boston City Hospital. Most of them were subject to epilepsy. A few were used more than once.

The following observations present data, a portion of which has already appeared in abstract form.⁴

TABLE 1.—Average Measurements of Blood Gases from Various Vessels

Number of Observations	Artery				Internal Jugular Vein				Cubital Vein				External Jugular Vein				Femoral Vein			
	Oxygen				Oxygen				Oxygen				Oxygen				Oxygen			
	Content	Capacity	Percentage Saturation	CO ₂ Content	Content	Capacity	Percentage Saturation	CO ₂ Content	Content	Capacity	Percentage Saturation	CO ₂ Content	Content	Capacity	Percentage Saturation	CO ₂ Content	Content	Capacity	Percentage Saturation	CO ₂ Content
14	18.5	20.5	90	49.6	12.4	19.8	62	56.2	14.0	19.6	71	53.8	16.8	20.3	83	51.6	14.0	20.1	70	53.3
40	19.2	20.5	94	49.5	12.4	19.9	62	55.8	13.6	19.8	69	53.8	17.8	20.5	87	51.2				
51	18.6	20.1	92	49.2	12.1	19.1	63	55.2	13.6	19.4	70	53.4								
60	12.6	19.9	63	54.9	13.5	19.8	68	53.2								

RESULTS

The average results obtained are shown in table 1. In fourteen subjects, blood was secured from five vessels. Average values in these instances for the percentage saturation of the blood with oxygen and its carbon dioxide content are shown graphically in chart 1. It will be seen that the values for venous blood obtained from a cubital and from a femoral vein were essentially the same. The surprising contrast was in the blood from the two jugular veins. That from the external jugular approached the composition of arterial blood, whereas that from the internal jugular was more "venous" than blood from the arm.

These results were so unexpected that a much larger series of observations was made in which blood was drawn from four vessels. The

3. Van Slyke, D. D.: Portable Form of Manometric Gas Apparatus and Certain Points in Technique of Its Use, *J. Biol. Chem.* **73**:121 (May) 1927.

4. Lennox, W. G.: Observations Concerning Intracranial Circulation in the Human Subject, *J. Clin. Investigation* **7**:517 (Aug.) 1929.

of the hand is also but little reduced.⁵ It would be of interest to know whether the blood which drains the face and scalp in animals is so nearly arterial.

We were not prepared to find such a low oxygen content of blood in the internal jugular veins. One might suppose that the brain, above all other tissues, would be so abundantly supplied with oxygen that blood leaving the cranium would carry a large unused amount. The relatively low oxygen saturation of blood in the internal jugular vein means either an unusually high rate of oxygen consumption in the brain or a slow rate of blood flow, or both. Observations that we are making should throw some light on the relative importance of these two factors. The difference in oxygen content of blood entering and leaving the brain in our patients (6.5 per cent by volume) was almost the same as the difference reported for rabbits (6.9 per cent by volume).⁶

THE RESPIRATORY QUOTIENT

Doisy and Beckmann⁷ pointed out that for a portion of the body a value for the respiratory quotient can be arrived at by dividing the increase in the carbon dioxide content of the venous blood by the decrease in its oxygen content, with reference to the carbon dioxide and oxygen content of arterial blood. Himwich and Castle⁸ corrected the formula to allow for any change in the concentration of the blood that might occur in its passage through the tissues. For a group of anesthetized dogs, they obtained an average respiratory quotient of 0.71 for isolated muscles deprived of skin and subcutaneous tissues, and a quotient of 0.77 for the intact leg.

Individual measurements are not of value because of alterations in the carbon dioxide content of blood associated with changes in breathing, in acid base relations or in the rate of diffusion of oxygen and carbon dioxide through the skin. We calculated the respiratory quotients for the average measurements obtained in our patients, correcting the quotients for changes in concentration of the blood. In a series of fifty-one observations, the average respiratory quotient for blood from the arm was 0.84, for blood from the brain, 0.9 and (in a smaller

5. Goldschmidt, S., and Light, A. B.: Method of Obtaining from Veins Blood Similar to Arterial Blood in Gaseous Content, *J. Biol. Chem.* **64**:53 (May) 1925.

6. Yamakita, M.: The Relation of the Blood Flow to the Gaseous Metabolism of the Brain, *Tohoku J. Exper. Med.* **3**:556 (Dec.) 1922.

7. Doisy, E. A., and Beckmann, J. W.: The Relations Existing Between Arterial and Venous Blood of the Dog with Special Reference to the Plasma Chlorides, *J. Biol. Chem.* **54**:683 (Dec.) 1922.

8. Himwich, H. E., and Castle, W. B.: Studies in the Metabolism of Muscle; I. The Respiratory Quotient of Resting Muscle, *Am. J. Physiol.* **83**:92 (Dec.) 1927.

There were great individual variations in the relationship of the blood from the internal jugular vein to that from the veins of the arms. In some persons blood from the internal jugular vein had the higher percentage saturation with oxygen, and in many patients blood from the two sources was practically the same. From patient to patient and from time to time the gaseous content of blood from the internal jugular was more constant than that from the cubital vein. We are endeavoring to determine factors which influence the differences observed.

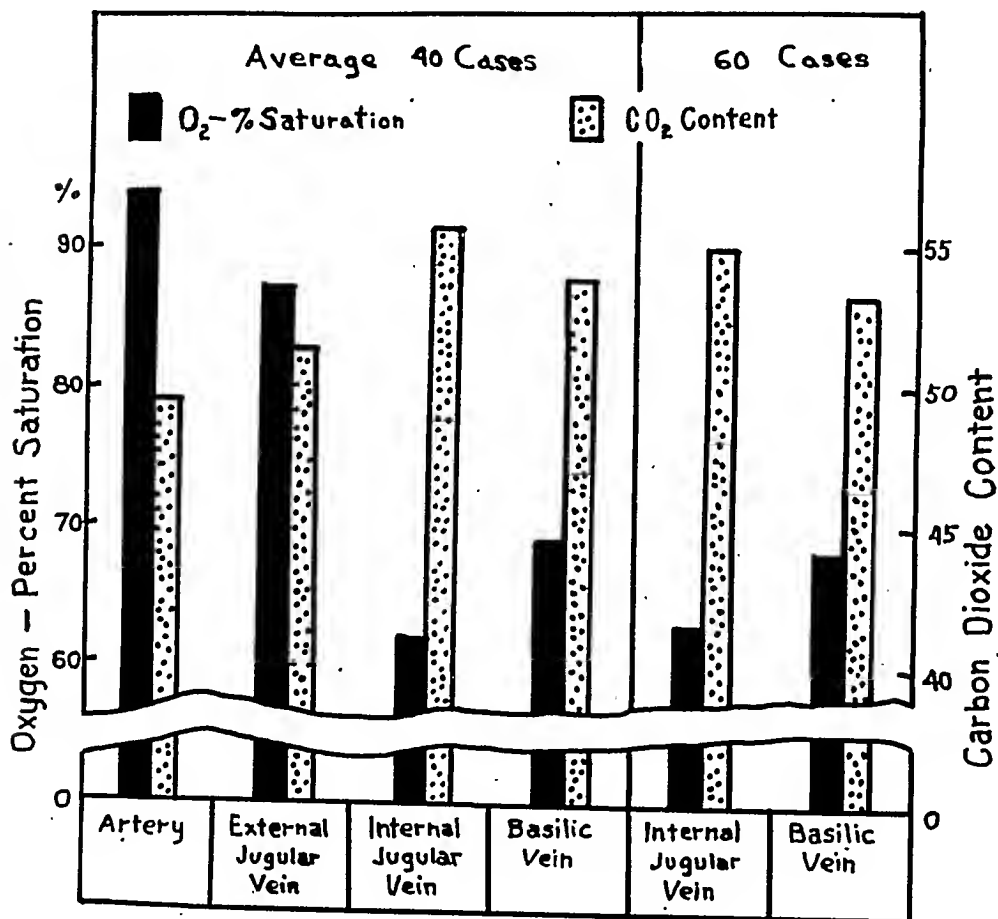


Chart 2.—The left hand portion of the chart gives the average results in forty cases, and the right hand portion the average results in sixty cases. The columns and the ordinates are the same as in chart 1.

We were not surprised to find that blood from the external jugular vein is nearly arterial. The tissues of the face and scalp are richly supplied with vessels. The metabolic rate of the skin and subcutaneous tissue is presumably low. One wonders to what extent the overabundant blood supply of the face with the resulting "complexion" may be the result of natural selection. Another factor may be the need of keeping an exposed surface of the skin warm. Blood from the veins on the back

external jugular vein. In single observations the difference of 4.5 mg. (about 5 per cent) in the blood coming from the arm and that coming from the brain would be of no significance, but as an average value, representing a fairly consistent individual difference, we believe that it is of significance. It is possible, of course, that the increased consumption of sugar is related to a decreased rate of blood flow through the tissues. This idea finds some support in the fact that the bloods which were low in sugar were also low as regards their saturation of oxygen. On the other hand, the sugar content of the internal jugular blood, in comparison with its oxygen saturation was disproportionately low. Because in making these observations we are not able to measure the blood flow or the metabolic rate of the brain, we cannot say that the observed increase in the respiratory quotient was accounted for by the observed increase in consumption of sugar. The observations indicate merely that both the respiratory quotient and the sugar consumption of the brain are a trifle higher than those of the superficial tissues of the arm.

SUMMARY

In a large series of patients, we measured the oxygen and the carbon dioxide content of the blood from an artery and from various veins. The gaseous content of blood from the femoral vein was found to be the same as that of blood from a cubital vein. In sharp contrast, blood from the internal jugular vein was more reduced and blood from the external jugular less reduced than from a cubital vein. These statements are true for average values. Measurements for individual patients varied widely.

In a series of fifty-one patients, the average corrected respiratory quotient for blood from a cubital vein was 0.84 and from the internal jugular vein, 0.9. More sugar disappeared from the blood in its passage through the brain than in its passage through the arm. The former of these observations suggests that in the metabolism of the human brain, carbohydrates are unusually important.

series of forty cases) for blood from the face, 1.2. Judging from Himwich and Castle's observations, skin and subcutaneous tissue would seem to have a comparatively high quotient. The fact that the superficial veins at the elbow derive their blood in large degree from skin and subcutaneous tissue might account for quotients somewhat more elevated than those of Himwich and Castle, in whose experiments blood was obtained from the femoral vein. The external jugular vein likewise drains a skin area. It is doubtful, however, whether significance can be given to this very high quotient, because blood from the external jugular vein differed so little from arterial blood. The respiratory quotient of 0.9 for the brain may be compared with a value of 0.86 determined by Loebel⁹ by means of the apparatus of Warburg for the gray matter of the brains of two rats, and with a value of 1 for anesthetized dogs by Himwich and Nahum.¹⁰

The chief interest, however, lies not in the absolute values obtained, but in a comparison of the quotients for the arm and the brain. In Himwich and Castle's experiments, muscle seemed to have a quotient

TABLE 2.—*The Average Oxygen Saturation and the Average Sugar Content of Blood from Various Vessels, in Twenty-Five Cases*

Source of Blood	Percentage Saturation With Oxygen	Sugar Content, Mg. per 100 Cc.
Artery.....	94	96.4
External jugular vein.....	87	94.4
Cubital vein.....	67	93.2
Internal jugular vein.....	62	88.7

lower than skin and muscle; in our observations, the brain had a higher quotient than the arm. This higher quotient suggests a relatively higher consumption of carbohydrate in the metabolism of the brain. This suggestion makes observations with regard to blood sugar of interest. Myerson and Halloran,¹¹ in a large group of psychotic patients, found that values for sugar in the blood tend to be lower for the internal jugular than for the cubital vein. In twenty-five experiments, we measured blood sugar as well as blood gases. The average results are shown in table 2. The average decrease of sugar in venous, as compared with arterial, blood was 7.7 mg. per hundred cubic centimeters for blood from the internal jugular vein, 3.2 mg. for blood from a superficial vein of the arm and 2 mg. for blood from the

9. Loebel, R. O.: Beitrag zur Atmung und Glykolyse tierischer Gewebe, *Biochem. Ztschr.* **161**:219, 1925.

10. Himwich, H. E., and Nahum, L. H.: Respiratory Quotient of the Brain, *Proc. Soc. Exper. Biol. & Med.* **26**:496, 1929. More extensive observations will be published elsewhere.

11. Myerson and Halloran: Personal communication to the authors.

are also relieved from allergic attacks in the allergen-proof chamber. Of course this relief lasts only as long as the patient breathes air that is free from allergens, just as the influence of high altitude ceases as soon as the patient goes back to low-lying districts. It has been proved, however, that the principle of the allergen-proof chamber may also be used for effecting permanent relief by the construction of allergen-proof chambers in the private house of the patient. Our results with this method have been published more extensively elsewhere.

During our work on the treatment for allergic diseases with allergen-proof chambers, we realized that the principle of this treatment might be extended to other diseases, and the first other disease to be studied was pulmonary tuberculosis. Our attention had been drawn to this disease by the circumstance that some patients with asthma combined with tuberculosis applied for admittance to our clinic, and did extremely well. They were relieved not only of their asthmatic attacks, but also of their pulmonary tuberculosis in a relatively short time. These cases, although not large in number, were the more impressive since the patients had been treated before in sanatoriums with little success in our low altitude. These observations brought us to the realization that the beneficial influence of high altitude in such cases of asthma combined with tuberculosis would have to be ascribed to the lack of climatic allergens in air at a high altitude. Then we were confronted with this problem: Why does high altitude cause improvement in cases of pulmonary tuberculosis uncomplicated with asthma? A brief survey of literature on the subject did not give satisfactory information. Neither lack of oxygen nor irradiation with ultraviolet light nor dryness of the air seemed adequate therapeutic factors, and we concluded that probably purity of the air—a factor repeatedly suggested by various authors but never generally accepted—would prove to be the most important therapeutic agent of high altitude; we included in this conception the supposition that in this case purity of air would mean lack of climatic allergens.

Since we had at our disposal a clinic with allergen-proof chambers and facilities for the ventilation of these chambers, either with outside air or with air purified by cooling, we could easily put our theory to an experimental test. Researches along this line have now been performed in our clinic for more than three years, and the results have entirely convinced us of the correctness of our theory.

In judging these results, our cases of pulmonary tuberculosis uncomplicated with asthma may be divided into three groups.

The first group contains light cases with apical or subapical catarrh, a temperature below 38 C. (100.4 F.), a pulse rate below 100, little sputum or no sputum at all, and if sputum is present, an absence of tubercle bacilli. It is known that such cases as a rule clear up quickly,

PULMONARY TUBERCULOSIS

TREATMENT IN ALLERGEN-PROOF CHAMBERS *

W. STORM VAN LEEUWEN
LEIDEN, HOLLAND

Seven years ago I suggested the theory that the undeniable influence that high altitude exercises on asthma and other allergic diseases is due to the absence of climate allergens in these regions. The correctness of this idea was proved by the demonstration of the fact that the effect that high altitude has on these diseases may be obtained in low-lying districts and in moist climates simply by technical methods, which involve the construction of a so-called allergen-proof chamber in the house of the patient. We have shown that "climate" in relation to allergic diseases is for the most part related to the condition of the soil, and that a moist soil with high absorbing power for water and a high level of ground water is unfavorable for patients with asthma, whereas a dry soil (sand, rock, chalk) with a low water capacity and a low level of ground water is favorable. Moreover, it was shown that the moist soil exerts its bad influence for the most part by favoring the conditions for the growth of micro-organisms in the house, i. e., in carpets, rugs, furniture, floors and walls and probably also under the floors. The climate allergens formed outside of the house are less active.

These considerations led to the conclusion that the sufferer from climate allergy may be brought into an almost normal condition by protection against the allergens prevailing in the air in his own house. This condition may be realized by the building of a small chamber in the bedroom of the patient, constructed of an asbestos material (eternite), which prevents the growth of micro-organisms. The simple type of these chambers is ventilated with air from a height of 30 feet (9.1 meters) above the roof of the house or even from outside a window blown into the chamber through metal pipes by means of a ventilator. The air is heated before it enters the chamber. In some cases the outside air has to be purified, which is done by cooling so that it loses the greater part of its water; this process of condensation removes the impurities from the air.

My co-workers and I have used this method of treatment in more than, 1,000 cases of asthma, and we have found that exactly the same percentage of patients who are benefited by residence in high altitude

*Submitted for publication, March 14, 1930.

*From the Pharmacotherapeutical Institute of the University and the Clinic for Allergic Diseases.

(100.2 F.). Shortly after admission she had an attack of influenza; five weeks after admission her temperature was normal, and she had no sputum nor râles. Sedimentation time was normal. After four months she left the clinic without any pathologic sign. She applied at another hospital for a position as nurse and was accepted.

CASE 4.—Gr., a man, aged 26, was treated for pulmonary tuberculosis in a sanatorium for more than a year without showing any improvement. He had suffered from asthma. On admission to our clinic he weighed 85 Kg. (187 pounds), but felt weak; the temperature varied between 36.5 and 37.7 C. (99.8 F.); on the right side of the thorax, moist râles were heard at the apex, and also in the axillary line and under the scapula; the sputum amounted to 20 to 40 cc. daily, and contained tubercle bacilli.

Treatment in the clinic caused improvement in breathing after one or two weeks. The amount of sputum diminished after three weeks; from that time no more tubercle bacilli were found. After three months the temperature was normal, there was no sputum or râles, and the patient was allowed to be out of bed for four hours; he went outdoors for one hour daily.

He then suffered from influenza, with a high temperature, an increased amount of sputum, moist râles, but no tubercle bacilli. Recovery was slow, but several months after admission to the clinic he left in perfect condition, with a normal temperature and raising no sputum; the moist râles had disappeared. He was completely fit to take up his work again. The sedimentation time was 17; it had been as high as 29 three months previously.

The second group of patients with tuberculosis contains relatively light cases, and the third group the severe cases. For the sake of convenience, the last group will be considered first.

In the acute forms of this group we see caseous pneumonia and in the chronic forms large cavities, sometimes accompanied or followed by caseous pneumonia. A high temperature, a high pulse rate and large masses of sputum with large quantities of tubercle bacilli are generally found here. The allergen-proof chamber cannot cure these patients. Such cases are not cleared up by residence in high altitude; indeed, high mountain air may even be noxious to the patients, so that they are not even admitted to sanatoriums in high altitudes.

It may be remarked, however, that in these cases the allergen-proof chamber has one special advantage above sanatoriums in high altitudes. Sanatoriums situated at a height of about 3,000 to 4,000 feet may, in severe cases of pulmonary tuberculosis, do harm to the patient; the allergen-proof chamber can never do any harm. We have observed some patients who could not stand the very dry air that is often used to ventilate the chamber. This disadvantage may be eliminated by a single manipulation which turns a valve in our ventilation system and offers simple outside air to the patients. Moreover, the dry air may easily be moistened.

The fact that, unlike high altitude, the allergen-proof chamber can never do any harm enables one to try the effect of residence in this chamber in almost every case of pulmonary tuberculosis, so that the

if rest, good food and good air are obtained; high altitude gives excellent results in these cases. Our experience with this group was, without exception, good. Residence in the allergen-proof chamber with purified air resulted in a quick disappearance of local and general symptoms. This disappearance of symptoms sometimes was realized in such a short time that I strongly doubt if all of these cases—although for the most part they were sent to us by competent specialists, who could support their diagnosis with roentgen examination—may be considered as cases of true tuberculosis. I incline to the view that a number of these patients suffered from a disease due to humid climate, i. e., hypersensitiveness to climatic allergens, which in these cases do not produce the ordinary symptoms of asthma or vasomotor rhinitis, but “low fever,” coughing, râles in the apex of one or both lungs and signs of induration or cicatrization in the roentgenogram. As has already been noted, these cases clear up quickly in the allergen-proof chamber. In the absence of tubercle bacilli the absolute proof of the origin of the disease often cannot be given, and I doubt whether it is wise to bring those patients to a sanatorium that houses cases of open tuberculosis, on account of the risk of infection.

The patients described are sometimes “cured” after residence in the clinic. Sometimes, however, the symptoms reappear after the patient returns to his former surroundings. In such cases, the condition of the patient’s home will have to be changed, as was fully described in my paper on social work in the treatment for asthma.

Examples of cases belonging to the first group follow:

CASE 1.—S. Z., a girl, aged 10 years, remained subfebrile after recovery from scarlatina; she coughed and showed signs of catarrh of the apex of the right lung. A specialist diagnosed the condition tuberculosis and considered the patient dangerous for her brothers and sisters. The Pirquet reaction was positive. On admission to the clinic the patient had râles at the apex, considerable coughing, and a maximum rectal temperature of 37.5 C. (99.5 F.). After residence in the allergen-proof chamber for ten days, she had a temperature of 37 C. (98.6 F.), she did not cough, and she had no pathologic signs on percussion or auscultation; she left the clinic after two months, completely recovered.

CASE 2.—Tr., a girl, aged 11 years, had a condition almost identical with that in case 1. She stayed in the clinic for six weeks and left completely recovered. This was probably a case of climatic allergy without tuberculosis.

CASE 3.—Cha., a woman, aged 22, had bronchitis and hemoptysis three years before admission to the clinic. She also suffered from hay-fever. She rested at home for three months, then spent six months in a tuberculosis sanatorium and, later one year in same sanatorium. No improvement occurred. She was sent to our clinic with a diagnosis of pulmonary tuberculosis of the apex of the left lung.

On admission, she had râles at the apex of the left lung, the sputum was negative for tubercle bacilli, and the maximum temperature was 37.9 C.

Examples of some cases of the second group of pulmonary tuberculosis uncomplicated with asthma follow.

CASE 5.—Gr., a woman, aged 21, had been treated at home for six months for pulmonary tuberculosis; the condition was regressive. On her admission to the clinic, extensive tuberculous bronchitis was found on both sides; she had moist râles over the entire right side, a maximum temperature of 38.2 C. (100.7 F.), and sputum amounting to about 100 to 150 cc. daily which was positive for tubercle bacilli; her weight was 55 Kg. (121.2 pounds). After fourteen days' residence in the allergen-proof chamber, she showed marked improvement; after five weeks, her temperature was generally 37.3 C. (99.1 F.), rising only occasionally to 37.5 C. Sputum amounted to 60 cc. and was positive for tubercle bacilli. The patient weighed 56.5 Kg. (124.5 pounds). Three months after admission she had a temperature of 37.3 C. and from 35 to 50 cc. of sputum showing no tubercle bacilli; the condition in the chest had cleared up considerably, and the patient weighed 60 Kg. (132.2 pounds).

One year after admission the patient left the clinic feeling completely well and able to do her work; her temperature had been normal for many months. Sputum amounted to 30 cc. and was negative for tubercle bacilli; except for a small cavity on the right side, there were no pathologic signs in the lungs.

CASE 6.—Wi., a woman aged 23, had suffered from tuberculosis for about two months before admission to the clinic. Her brother had been treated for tuberculosis in our clinic with complete success. Tuberculosis of the apex of the left lung was found and the sputum was positive for tubercle bacilli; the temperature was normal. There were moist râles in the apex of the left lung and dry râles in the apex of the right.

In the allergen-proof chamber she showed rapid improvement. After three weeks there was no coughing or sputum, the moist râles had disappeared, and dry râles were heard only occasionally. Six months after admission she was completely well. After leaving the clinic, she resumed her profession as teacher.

Although nobody doubts that residence in high mountain air has a beneficial influence in many cases of pulmonary tuberculosis, every one will admit that high mountain air does not bring the ultimate solution of the problem of tuberculosis. But there is also no doubt about the fact that the campaign against tuberculosis would be much more effective if high mountain air could be available for all patients with pulmonary tuberculosis who might be benefited by it. This, of course, will never be attainable, and it is for that reason that I emphasize the importance of the fact that by relatively simple and not too expensive technical methods everything that high mountain air might offer for the improvement of the tuberculous patient may be obtained in any place and in any climate. The advantage of the new method does not stop here. High mountain air is wonderful in certain periods of the year, but may be very cold and moist and distinctly disagreeable during other periods; moreover, in certain cases of pulmonary tuberculosis it may actually do harm to the patient. All those disadvantages are eliminated by the "artificial high mountain air" which the allergen-proof chamber offers. Conditions with reference to temperature, humidity and purity of the air may be kept constant for weeks and months.

line drawn between the second and the third group need not be very sharp, and many patients who could not risk a trip to a high altitude might be allowed a trial in the allergen-proof chamber. Consequently, the number of patients who may be given a chance of cure is enlarged.

The most important group of patients with tuberculosis, from the therapeutic point of view, consists of those who suffer from open tuberculosis of the lungs, with symptoms of bronchitis or small cavities, a temperature up to 38 C., a pulse rate up to about 100, a fair amount of sputum containing tubercle bacilli and tuberculous lesions that may be clearly demonstrated by roentgen physical examination, but who still offer fair possibilities of a cure.

Almost all of these patients show definite subjective and objective signs of improvement during the first weeks or months after admission, and it is our experience that if improvement occurs at all, it starts within the first three or four weeks. Patients who have not shown definite improvement after two months are considered by us as inappropriate for treatment in the allergen-proof chamber, and are advised to go home.

In cases that show improvement, the first salutary symptom, as a rule, is diminution of coughing and more ease in breathing. This form of improvement is often experienced by the patient during the first two or three days, and we have learned to consider this a good omen. Along with the improvement in breathing and relief from coughing the temperature and pulse rate may become lower; usually this occurs after three or four weeks; simultaneously the quantity of sputum may or may not decrease. As a rule, the body weight increases considerably, and the general condition of the patient improves.

As has been mentioned, we observe this initial improvement in the patient's condition in most of the cases of this group, sometimes even in patients whose condition has to be considered as incurable, and who ultimately die in the clinic.

The initial improvement may continue and lead to a definite improvement or to a cure of the patient, or it may come to a standstill. In the last instance we have at least obtained a temporary relief, reduced the suffering of the patient considerably and probably lengthened his life. Most of these patients remain on this level till an acute intermittent infection, often an attack of influenza or "cold" throws the balance to the unfavorable side.

It should be remembered that all the observations mentioned are related to treatment in the allergen-proof chamber only, all other therapeutic measures, including excessive feeding, being excluded during the first two months of observation; drugs are given only when the patient has been accustomed to take them, and even then we try to reduce the amount as soon as possible. Active therapy is never started before the observation of the patient has been finished.

THE SPECIFIC EFFECT OF BILE SALTS ON PNEUMOCOCCI AND ON PNEUMOCOCCUS PNEUMONIA *

EDWIN E. ZIEGLER, M.D.
NORTHPORT, N. Y.

In 1900, Neufeld¹ discovered that pneumococci in suspension were dissolved by adding bile to them.

Since that time, others have shown that solutions of the bile salts, i. e., sodium glycocholate and sodium taurocholate acted in the same way, and that whole bile was not necessary. In fact, there is evidence that the cholate part of the molecule is really the active part causing the lysis. This is one of the classic tests for the identification of pneumococci.

It is interesting to watch Neufeld's phenomenon under the high power of the microscope. To obtain this, mix a drop of pneumococcus suspension and a drop of bile salt solution on a glass slide, placing a cover-slip glass on it. The pneumococci gradually dissolve, becoming smaller and smaller. They pass through the stage in which they exhibit the brownian movement, and finally disappear.

Bile-solubility was found by Schilling² and Neufeld¹ to be a characteristic of trypanosomes and spirilla as well as of pneumococci. Knowing the specific action of quinine on spirilla and trypanosomes, certain workers were led to try quinine and some of its derivatives in the treatment for pneumonia. Along this line of reasoning, ethylhydrocuprein was developed.

Since pneumococci are soluble in solutions of bile salts, my co-workers and I thought of using the bile salts themselves in the treatment for pneumonia. This paper deals with the treatment for pneumonia by the bile salts, sodium taurocholate and sodium glycocholate, with some laboratory experiments on the salts and their properties.

EXPERIMENTAL WORK

In our work we found that suspensions of pneumococci are lysed by sodium taurocholate (Merck) in extremely dilute solutions. (This product, called sodium taurocholate 50 per cent by the manufacturer, is stated to run between 45 and 55

* Submitted for publication, March 6, 1930.

* From the U. S. Veterans' Hospital.

1. Neufeld: *Ztschr. f. Hyg. u. Infektionskrankh.* **34**:454, 1900; *Arb. a. d. k. Gsndhtsamte.* **25**:494, 1907.

2. Schilling: *Centralbl. f. Bakteriöl.* **31**:452, 1902.

The accompanying chart gives the course of the relative humidity during a period of five days in one of our allergen-proof chambers, ventilated with cooled air. On the left side of the curve is shown the relative humidity in one of the other rooms of the clinic not ventilated by special arrangement, so as to show the great difference in humidity between an ordinary room and an allergen-proof chamber.

In cases of asthma, residence in allergen-free air is helpful only as long as the patient is kept in these allergen-free surroundings. In pulmonary tuberculosis, however, a real cure may be effected by residence in the allergen-proof chamber for several months or a year. After this period it is still preferable for the patient to live in conditions which resemble those of the allergen-proof chamber as far as possible. This may be achieved either by the construction of an allergen-free chamber in the house of the patient or by changes in the patient's bedroom and other

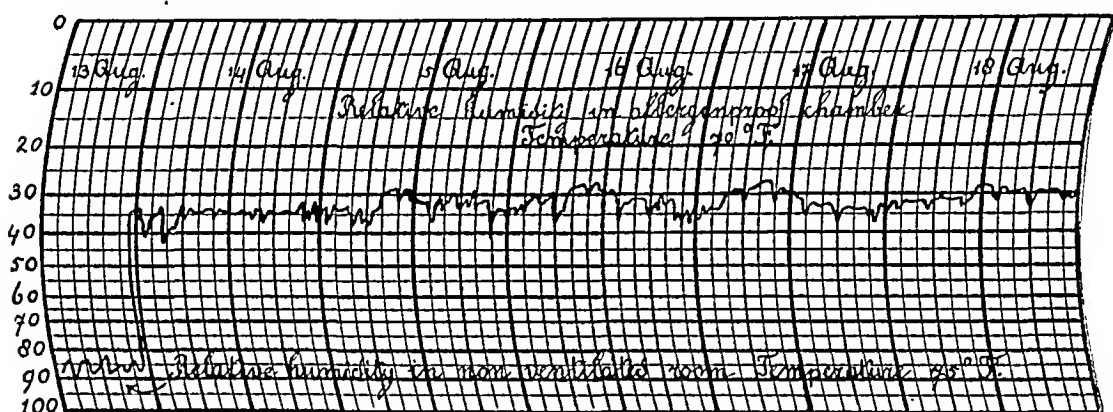


Chart showing the relative humidity in an allergen-proof chamber for five days. The small portion of the curve at the left indicates the relative humidity in another room of the clinic not ventilated by special arrangement.

rooms of the house. Both matters have been discussed by me in other papers.

The installation of an allergen-proof chamber in private houses has hitherto been seriously handicapped by the circumstances that: (1) the installation was rather expensive, and (2) the installation could be moved from one house to another only with difficulty and at considerable cost. Both difficulties have been met by the German constructor of the chambers, who found a device by which the chamber can be easily moved and placed in any room; moreover, he reduced the price considerably. In this way the allergen-proof chamber in the future will not only be a necessary addition to any clinic in which patients with diseases of the lungs or bronchi are treated, but will also become an important help in the treatment of patients at home, and thus become an instrument, not only of interest for the physician who works in clinics or sanatoriums, but also for the general practitioner.

table 3. Bile salts were added to human serum in a 10 per cent solution. To this "bile-serum," as it was called, we added equal parts of pneumococci suspension. This reduced the concentration of the sodium taurocholate to 5 per cent. We found that prompt lysis did not take place, but that there was sufficient clearing after an hour to detect lysis. After about eight hours the tubes were as clear as the controls. Controls were made with equal parts of "bile-serum" and 0.85 per cent sodium chloride. Controls by contrast were obtained by repeating the experiment and comparing the freshly prepared tubes with those of eight hours previously. In performing this experiment it is desirable to employ serums that do not contain agglutinins for pneumococci. Although interference with lysis did take place, the serum did not prevent lysis but merely delayed it, so that readings in these experiments had to be made up to twelve hours. It was found that Neufeld's phenomenon takes place slowly in the presence of serum.

TABLE 3.—*Neufeld's Phenomenon in the Presence of Human Serum**

Solution	15 Min.	1 Hr.	2 to 8 Hrs.	10 Hrs.
0.5 cc. bile-serum 10% plus 0.5 cc. Pneumococcus Suspension	Cloudy	Clearer	Clearer	Clear as control 1

Control 1 was obtained with 0.5 cc. of bile-serum plus 0.5 cc. of 0.85 per cent sodium chloride; control 2 with 0.5 cc. of bile-serum plus 0.5 cc. of pneumococcus suspension prepared at the time of comparison; this is the more obvious control by contrast. Bile-serum consisted of 10 per cent bile salts in human serum. The final concentration of bile salts was 5 per cent.

TABLE 4.—*Effect of Bile Salts on the Antibody Action of Specific Serums on Pneumococci*

	Bile Salts 10 per Cent in Homologous Serums, 0.5 Cc.	Bile Salt 10 per Cent in Indifferent Serums, 0.5 Cc.	Homologous Serums, 0.5 Cc.	Indifferent Serums, 0.5 Cc.
Pneumococci suspension, 0.5 cc.....	Agglutination	Cleared	Agglutination	Cloudy
Supernatant fluid from, pneumococci, 0.5 cc...	Precipitation	Clear	Precipitation	Clear

A group of experiments was designed to determine whether bile salts interfered with antibody action on pneumococci. It was found that they did not prevent the agglutination or precipitation tests with specific type serums. These results are given in table 4. Controls were run with serums that did not contain bile salts, so that we could be sure that the serums contained specific antibodies. Bile salts did not interfere with these antibody actions. The same results were obtained in a preliminary way in the work represented in table 2. These results are important in consideration of the fact that bile salts are being tried therapeutically. The supernatant fluid obtained by centrifugating the pneumococci out of suspension was used in the precipitation tests. Throughout all these experiments, an 0.85 per cent solution of sodium chloride was used consistently for a solvent in the preparation of suspensions and solutions. In investigating bile salts therapeutically, it would not be expected that they would interfere with natural antibody action. This assumption, of course, arises from the results of the foregoing experiments with agglutinating serum, pneumococci and bile salts.

As the cytolytic effect of bile salts was known, it was desirable to obtain a more definite idea of this effect on normal human blood cells. A dilution series of the bile salts was mixed with equal amounts of washed blood cells (10 per

per cent, the balance being chiefly the glycocholate with small amounts of the other bile salts. This is the product that was used in the following work and is what is meant when the term "bile salts" is used.) For a solvent we consistently used an 0.85 per cent solution of sodium chloride. We added serial dilutions (from 1:20 to 1:25,000) of sodium taurocholate to suspensions of pneumococci. Appropriate controls were made with salt solution. It was found that lysis does not depend on the concentration of the bile salts, Neufeld's phenomenon being present in the most dilute solution used. For prompt lysis the higher concentrations are needed. For the dilute solutions the readings were made at intervals, the tubes being kept in an incubator and shaken before reading. The most

TABLE 1.—*Lysis of Pneumococci by Bile Salts**

Solution	Result
50:1,000 (5.0%).....	Prompt clearing
20:1,000 (2.0%).....	Cleared within 10 minutes
10:1,000 (1.0%).....	Cleared within 10 minutes
8:1,000.....	Cleared within 30 minutes
6:1,000.....	Cleared within 30 minutes
4:1,000.....	Cleared within 30 minutes
2:1,000.....	Cleared within 30 minutes
16:10,000.....	Clearer within one hour
12:10,000.....	Clearer within one hour
8:10,000.....	Clearer within one hour
4:10,000.....	Clearer within one hour
2:10,000.....	Clearer within one hour
16:100,000.....	Clearer within two hours
12:100,000.....	Clearer within two hours
8:100,000.....	Clearer within two hours
4:100,000.....	Clearer within two hours

* The controls remained cloudy

TABLE 2.—*Lysis of Pneumococci in Tubes Containing Serum*

Pneumococci Suspension, Cc.	Plus Type Serum, Cc.	Precipitate	Plus Bile Salts,		Result
			Cc.	%	
0.5	0.5 1:5.....	No	0.5	10	Cleared
0.5	0.5 1:10.....	No	0.5	10	Cleared
0.5	0.5 1:20.....	No	0.5	10	Cleared
0.5	0.5.....	No	0.5 sodium chloride		Cloudy
0.5	0.5 (specific).....	Yes	0.5	10	Unchanged
0.5	0.5 sodium chloride....	No	0.5	10	Cleared

dilute solutions showed clearing when compared with controls, but did not become completely clear. This was interpreted as being due, not to the dilute solution, but to the small actual mass of bile salts available as compared with the number of organisms. The results of these tests are shown in table 1.

After determination of the type of pneumococci with specific serums, there were always a number of tubes in which agglutination, of course, did not take place. To these tubes were added solutions of biles salts, and lysis took place just as in the controls without serums. If bile salts were added to tubes in which agglutination had occurred, the clumps did not dissolve. These results are shown in table 2. It is interesting that the action of agglutinins on pneumococci makes them nonsoluble in bile salt solutions.

It is seen from the experiments represented in table 2 that serum does not prevent lysis of pneumococci by bile salts. Another group of experiments along this line was performed with human serum. These results are expressed in

pneumonia. He also demonstrated that in cases of crisis the highest icterus index occurred either the day before, the day of, or the day after, the crisis. Icterus usually occurred in the latent zone. Fatal cases showed relatively low icterus indexes. If a patient with pneumonia developed a pleural exudate (empyema), the icterus index returned to normal. Influenzal pneumonias did not cause an increased icterus index.

This work led us to assume that icterus in pneumococcus pneumonia was a defensive reaction of the liver on behalf of the body; the liver secreted the bile salts into the blood stream in these cases in an "effort" to damage the pneumococci or to aid in the unknown mechanism by which pneumonia is terminated.

On Jan. 7, 1930, we injected bile salts (sodium taurocholate, Merck) intravenously in a case of lobar pneumonia for the first time, and we have used these treatments in subsequent cases. The drug was dissolved in an 0.85 per cent solution of sodium chloride, filtered and autoclaved before using.

Sodium taurocholate was shown by Emerson⁴ to be the less toxic of the two salts. This was to be expected, as the taurocholate molecule contains a sulphate group ($C_{26}H_{45}SO_7N$), whereas the glycocholate molecule ($C_{26}H_{45}O_6N$) does not. Emerson found that the lethal dose of sodium glycocholate was 0.255 Gm. per pound of dog, while that of sodium taurocholate was 0.303 Gm. when given continuously until death.

Our highest therapeutic dose for man was about 0.05 Gm. per pound; and making a direct comparison, the fatal dose would be from five to six times as great as the one we used, or from 0.25 to 0.30 Gm. per pound. Our highest dose was 8 Gm., whereas the calculated fatal dose would be 40 Gm. The greatest total amount given any one patient was 29 Gm. in five days. The doses were 4, 5, 6, 8 and 6 Gm., respectively.

In making our first injections we used concentrated (10 per cent) solutions in a syringe. We found that this produced a chemical phlebitis, with discoloration along the veins and venous obliteration. Subsequent treatments were given with a gravity apparatus in concentrations of from 1 to 2 per cent.

No toxic effects from the drug were noticed. There was no bradycardia and no hemoglobinuria. Blood cell counts showed that some secondary anemia was produced. The respiratory rate seemed to be increased more than one would expect from the disease alone, although we could not be sure of this. We found that the treatments stimulated the flow of bile, causing frequent stools, so that constipation and typhinites did not occur.

Bile has been used from time immemorial as a therapeutic agent, but in recent years has fallen into disuse. The work represented in this paper may stimulate a new interest in bile and bile salts.

Castellanos⁵ reported the use of bile salts in treating three children for empyema. He injected the solution directly into the pleural cavity. He also treated a patient with meningitis and one with septicemia

4. Emerson, W. C.: *J. Lab. & Clin. Med.* **14**:635 (April) 1929.

5. Castellanos y Gonzales, A.: *Rev. de med. y cir. de la Habana* **34**:133 (Feb.) 1929; *Vida nueva* **23**:122 (Feb. 15) 1929.

cent). The cells were washed free from serum by centrifugation and resuspension in salt solution, three times. Table 5 shows the results with the lowest dilutions used. Dilutions from 1 to 5 per cent gave complete lysis within a few minutes. Those from 0.4 to 0.8 per cent gave complete lysis in between thirty minutes and one hour. Complete results with the lesser concentrations are shown in the table. Between readings the tubes were kept in an incubators at 37 C. During these intervals the red cells settled out of suspension to the bottom of the tubes. By the shade of the red in the supernatant fluid and the amount of precipitated cells, one could estimate the amount of lysis that had occurred. The tubes were then shaken and replaced in the incubator.

In comparing these results with those in experiments on pneumococci, represented in table 1, it was observed that bile salts are much more lytic for pneu-

TABLE 5.—*Lysis of Blood Cells in Bile Salts*

Bile Salts, %	Suspension of Blood Cells Plus Bile Salts			
	½ Hour	1 Hour	2 Hours	3 Hours
0.2.....	Slight lysis	Lysis	Lysis	Lysis
0.1.....	Slight lysis	Lysis	Lysis	Lysis
0.08.....	Slight lysis	Moderate lysis	Lysis	Lysis
0.06.....	Very slight lysis	Slight lysis	Lysis	Lysis
0.04.....	No lysis	Very slight lysis	Slight lysis	Lysis
0.02.....	No lysis	No lysis	No lysis	Slight lysis

TABLE 6.—*Effect of Serum on Cytolysis of Blood Cells by Bile Salts*

	Suspension Blood Cells, Cc.	Result	Centrifugation
Plain Nonhemolytic serum, 0.5 cc..	0.5	No hemolysis	Cleared with precipitation
Bile-serum 10 per cent, 0.5 cc.....	0.5	Hemolysis	Unchanged

mococci than, for red cells. A solution of 0.02 per cent showed only a trace of lysis after three hours in the case of the red cells, whereas a solution of 0.004 per cent (4:100,000) produced some lysis of pneumococci in two hours. Roughly, it can be calculated from this that bile salts are five times more lytic for pneumococci than they are for human blood cells ($0.02 \times 1/.004 = 5$).

Table 6 gives the results in an experiment showing that serum did not prevent cytolysis of blood cells by bile salts.

In order to determine whether serum had some specific protective effect on pneumococci we suspended these organisms in nonagglutinating human serums for fifteen minutes at 37 C. The suspension was then diluted with salt solution. The organisms were thrown down in the centrifuge and the serums poured off. The organisms were then resuspended in salt solution and dilutions of bile salts added. Lysis took place with these serum-exposed organisms just as it did with organisms not so exposed.

Elton³ has done some work with icterus index determinations in pneumonia. He showed that the icterus index was increased in a series of seventy cases of

3. Elton, N. W.: J. Michigan M. Soc. 28:451 (June) 1929; New England J. Med. 201:611 (Sept. 26) 1929.

The throat was moderately red. The next day there was pain in the left side of the chest; mucous râles were heard over the hili, and there were changed breath sounds over the upper left part of the chest. On January 4, there was definite dullness over the upper left part of the chest and other signs of consolidation. The sputum remained blood-streaked, with much pus present. On January 6, there were signs of extension of the consolidation to the entire left lung. On January 7, the patient's general condition was very unsatisfactory; he was restless and delirious. The entire left lung was consolidated. At 10:45 a. m., we gave the patient 1 Gm. of bile salts in 20 cc. of physiologic solution of sodium chloride. At 4:00 p. m. we gave the patient 3 Gm. of bile salts in 30 cc. of salt solution. On January 8, the patient's condition was somewhat improved, but his left lung remained consolidated. We gave him 4 Gm. of bile salts in 300 cc. of salt solution. On January 9, his condition was greatly improved. Râles of resolution were heard over the entire left side of the chest. At 10:30 a. m. he was given 6 Gm. of bile salts in 300 cc. of salt solution. On January 10, the patient continued to show improvement. On January 11, the clinical chart was normal. He remained well, except for his mental condition which showed little change.

Laboratory examinations by Dr. M. C. Terry showed: on January 2, red cells 4,850,000, hemoglobin 75 per cent, leukocytes 34,600 and polymorphonuclears 90 per cent; pneumococci and staphylococci were present in the sputum; on January 3, leukocytes 27,800 and polymorphonuclears 85 per cent; on January 6, leukocytes 21,800 and polymorphonuclears 82 per cent; on January 7, leukocytes 27,600 and polymorphonuclears 85 per cent; on January 20, red blood cells 2,870,000 and hemoglobin 60 per cent; on January 23, red blood cells 3,250,000 and hemoglobin 65 per cent. Other laboratory reports were negative, including Wassermann and Kahn reactions of the blood and the spinal fluid, urinalysis and examination of the stool.

CASE 2.—In the case of M. D., a white man, aged 33, 71 inches (180 cm.) in height and 162 pounds (73.5 Kg.) in weight, the diagnosis was pneumonia, bronchitis, septicemia and manic-depressive psychosis. On Jan. 5, 1930, the patient was received in the infirmary ward. He was quite ill, his face was flushed, his mouth dry, and there was a large amount of thick mucus in his pharynx. The sputum contained blood and pus. There was slight dullness over the upper left part of the chest and a roughening of breath sounds over the hili in the back. On January 6, a positive Kernig sign and a positive Babinski reflex on the left side developed. There was stiffness of the neck. A lumbar puncture was performed showing an initial pressure of 285; the fluid was clear; the Wassermann, Kahn and other tests were negative. Indefinite signs of pneumonia were observed in the chest. The sputum was still blood streaked. The patient's condition was considered grave. The x-ray report stated lobar pneumonia involving the base of the right lung (Dr. J. G. Cullins). On January 7, the patient's neck was stiff, but the positive Kernig sign had disappeared and the reflexes were normal. The sounds in the chest were still indefinite. The patient was brighter mentally. On January 10, the neurologic examination gave negative results. The eyegrounds were normal. The patient was slowly improving. On January 11, he was given 3 Gm. of bile salts intravenously. On January 12, he showed great improvement. He was given 6 Gm. of bile salts intravenously. On January 13, the patient's clinical chart had returned to normal, but he was given 4 Gm. of bile salts intravenously. His clinical chart remained normal. His convalescence was uneventful. The mental condition was unchanged. Laboratory reports furnished by Dr. M. C. Terry showed: On January 5, total leukocytes 17,000, polymorphonuclears 71 per cent, hemoglobin 80 per cent and red blood cells 4,180,000; the urine was normal;

intravenously. He reported good results in this work on the treatment of children for pneumococcus infections.

Having this evidence of the effect of bile salts, we felt justified in using the same treatment in lobar pneumonia in man.

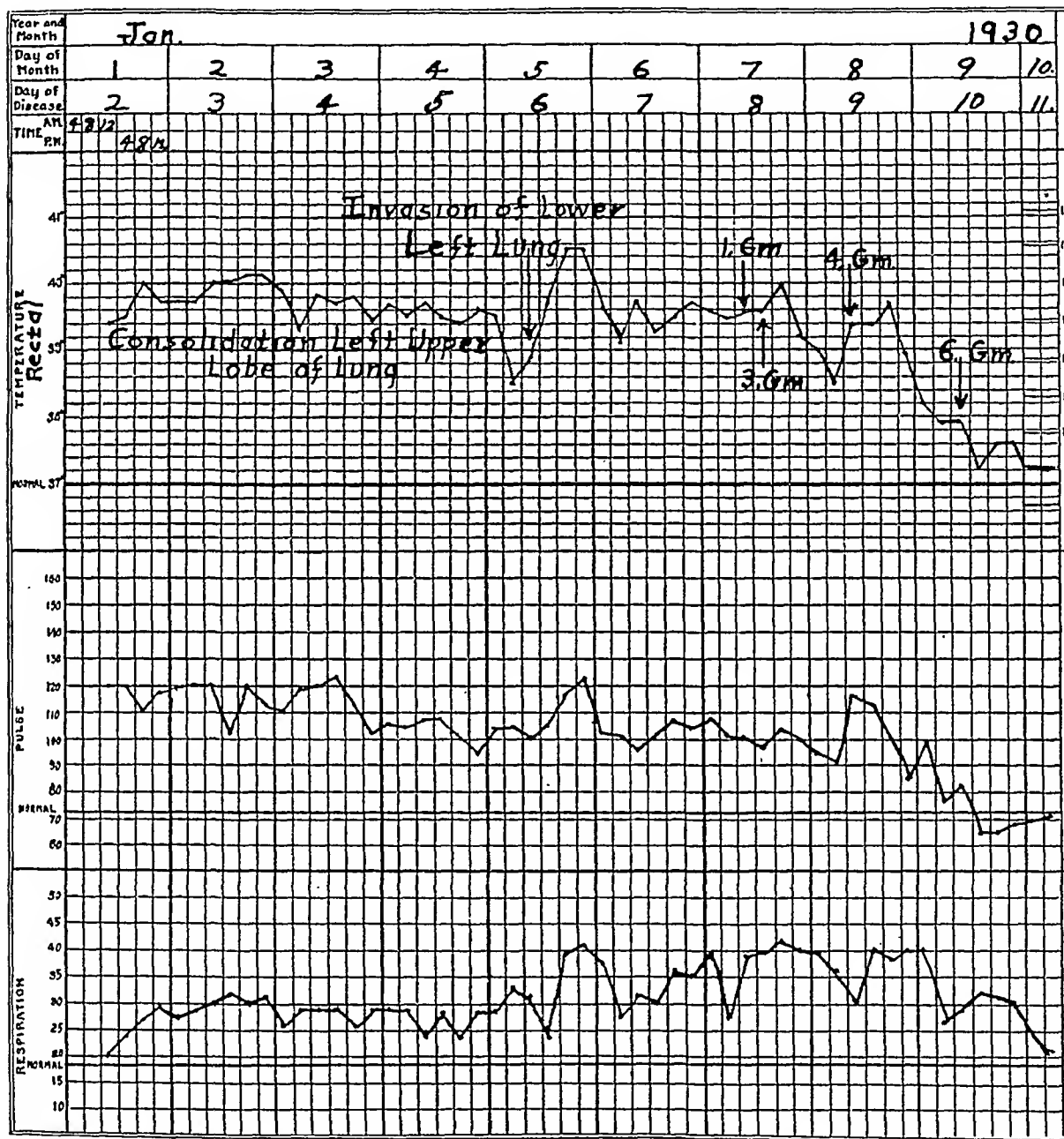


Chart 1.—Clinical data in case 1; dosage of bile salts is given in grams.

REPORT OF CASES

Several case reports follow.

CASE 1.—In the case of E. B., a white man, aged 32, 64 inches (162 cm.) in height and 120 pounds (54.4 Kg.) in weight, the diagnosis was lobar pneumonia and dementia praecox. On Jan. 1, 1930, the patient became ill with chills and fever. There was bronchitis, and the sputum was blood-tinged and contained pus.

the lower left part of the chest. There was tenderness over the upper left part of the abdomen, and pain was produced on palpation of the lower left ribs. On January 10, the patient was given 4 Gm. of bile salts. An x-ray picture of the chest showed increased cloudiness of the base of the left lung (Dr. J. G. Cullins). On January 11, consolidation of the entire left lung was noted. The patient was

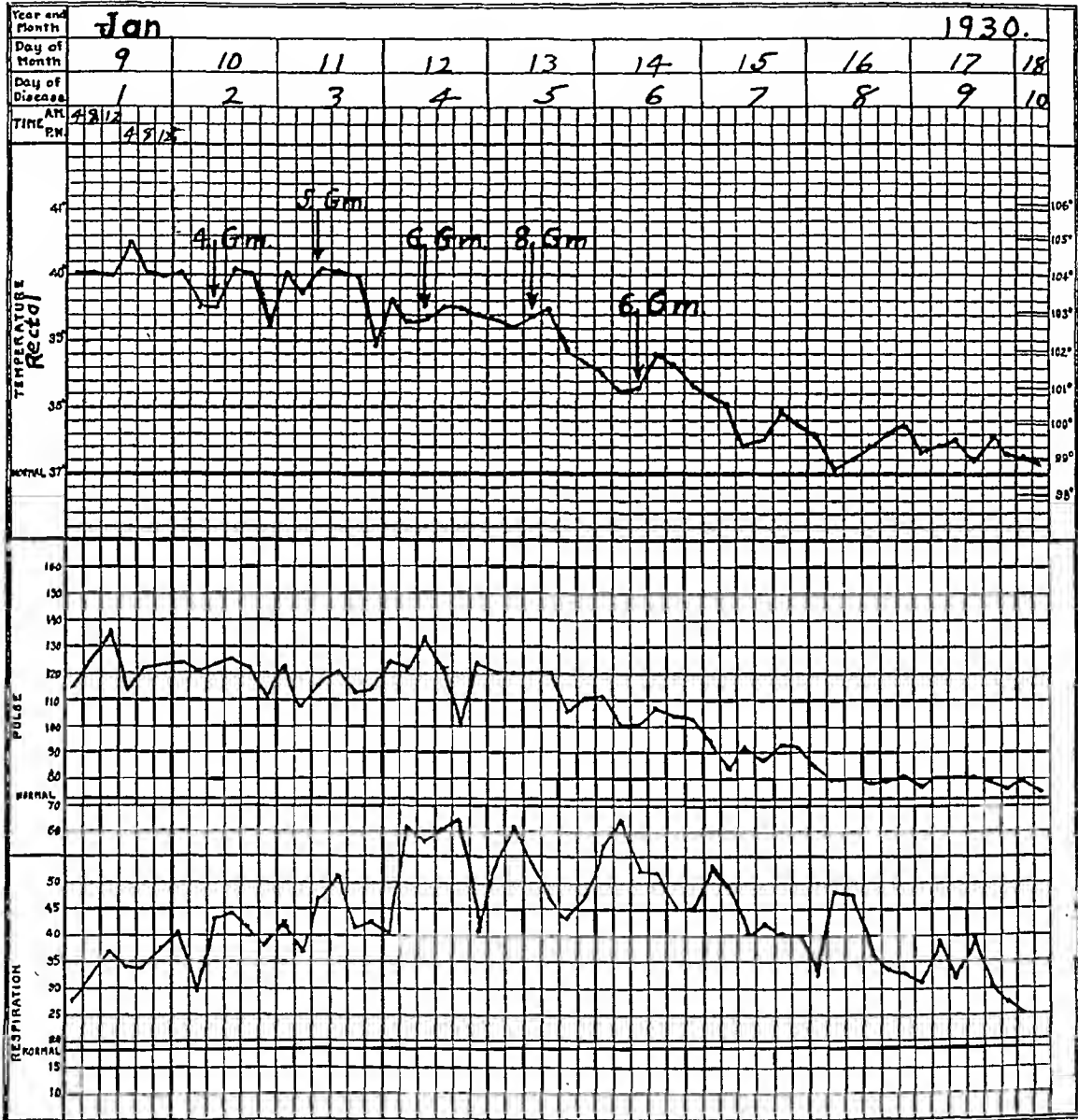


Chart 3.—Clinical data in case 3.

given 5 Gm. of bile salts intravenously. On January 12, he was very ill and semi-conscious. There was considerable abdominal rigidity. A pleural rub was heard on the left side as high as the fourth rib. Six grams of bile salts was given intravenously. On January 13, the patient's general condition was much improved. He was brighter mentally. His clinical chart showed improvement. Abdominal rigidity was almost gone, but he still complained of much pain in his left side. He was given 8 Gm. of bile salts intravenously. On January 15 the temperature

on January 6, leukocytes 23,400, polymorphonuclears 89 per cent; on January 11, pneumococci grown from a blood culture; on January 16, pneumococci from a culture was passed through mice agglutinated by type II serum; on January 20, red blood cells 3,670,000, hemoglobin 70 per cent and leukocytes 7,100; on January 23, red blood cells 4,180,000, hemoglobin 75 per cent and leukocytes 9,200; on March 5, red blood cells 4,200,000, hemoglobin 75 per cent and leukocytes 7,400.

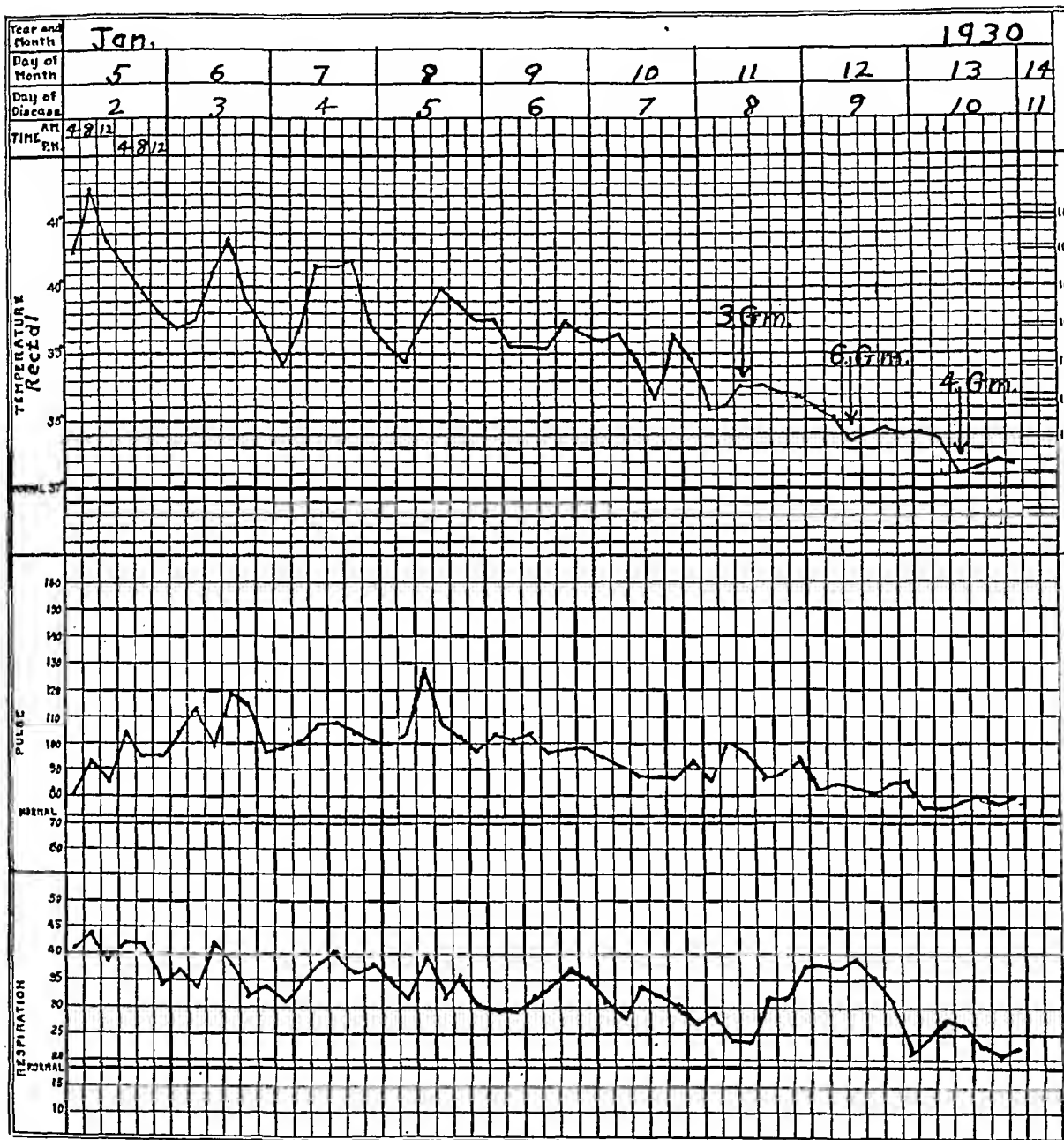


Chart 2.—Clinical data in case 2.

CASE 3.—In the case of J. M., a white man, aged 21, 68 inches (172 cm.) in height and 145 pounds (65.7 Kg.) in weight, the diagnosis was lobar pneumonia with pleurisy. The patient was admitted on Jan. 9, 1930, complaining of acute abdominal pain on his left side, which began the previous evening. He had chills and vomited during the preceding night; he presented the picture of an acute abdominal condition. There were, however, beginning signs of consolidation of

not to give another treatment in this case, to determine whether the temperature would remain normal. It remained normal with occasional slight elevations of about 1 degree which disappeared after a few days. No doubt, one more injection of bile salts would have been of benefit in this case.

Certain interesting relations were noted between the injections of bile salts and the temperature curve. Following each treatment the temperature would drop, reaching its lowest point from twelve to twenty-four hours after injection of the drug. Temperature readings were made hourly during the daytime following each treatment. This showed that there was a reaction to the drug lasting from one to three hours. The temperature would increase about a degree for this period of time and then would decrease.

The treatments seem to have a tendency to flatten out the temperature curve by removing its erratic fluctuations. The only fluctuations of any extent noted in the curves after treatment, were downward, in contradistinction to upward fluctuations noted in those parts of the curve made when the bile salts were not given.

COMMENT

Further work on this subject is in progress. Lysis of pneumococci by bile salts takes place in serum. The effect of the serum is greatly to retard the speed with which lysis takes place. It is also found that bile salts cause a lysis of blood cells in serum, as well as in salt solution. We have found, as Tatum⁶ and others have, that bile salts are cytolytic. They dissolve cells other than pneumococci, namely, blood cells, spirilla, trypanosomes; and probably endothelial and other types of cells.

We have found that bile salts are approximately five times more lytic for pneumococci than they are for blood cells. Considering this fact with the observation that clinical administration produces some anemia, it is reasonable to conclude that bile salts have a lytic action on pneumococci in vivo. That bile salts produce a slight secondary anemia is no contraindication to their use, in consideration of the fact that they aid in the termination of the pneumonic process.

That bile salts are not inert in the human body is shown by the facts that we have observed, namely: They tend to terminate the course of pneumococcus pneumonias; they seem to have a lytic effect in the body on red blood cells, producing a mild anemia; they cause an increased output of bile, and in certain concentrations they damage the veins.

We have shown that bile salts do not prevent antibody action; for when they are added to the specific antisera, the agglutination and

6. Tatum, A. L.: J. Biol. Chem. 27:243, 1916.

became normal for the first time, although it had begun to fall on January 11, which was the third day of the disease (following the second dose of the drug), in spite of the fact that the entire left lung had just become consolidated. Consideration of the temperature curve in relation to the dosage given is significant. A final dose after the temperature became normal was not given in this case to note the effect on the temperature curve. The curve became slightly erratic as before the treatments were given, but remained essentially in the normal range between 99 and 100 F. After January 16, the temperature was consistently normal—not above 99.6 F. The respiration was very rapid, seemingly due to the pleurisy. Sounds of dry pleurisy were the last symptoms to clear up. Convalescence was normal. This patient was a hospital employee.

Laboratory reports by Dr. M. C. Terry showed: on January 9, normal urine; many gram-positive diplococci and possibly pneumococci in the sputum; leukocytes 34,500 and polymorphonuclears 90 per cent; on January 10, normal urine; pneumococci predominating in the sputum; on January 11, leukocytes 13,500 and polymorphonuclears 86 per cent; normal urine with no hemoglobinuria; on January 13, leukocytes 13,800 and polymorphonuclears 85 per cent; on January 14, red blood cells 4,950,000, hemoglobin 75 per cent, leukocytes 18,100 and polymorphonuclears 81 per cent; normal urine, with no hemoglobinuria; on January 16, normal urine, with no hemoglobinuria; organisms from the sputum, passed through mice, were agglutinated by specific serums of type II; on January 23, red blood cells 3,250,000, hemoglobin 65 per cent and leukocytes 8,500; on March 1, red blood cells 4,400,000 and hemoglobin 85 per cent.

It will be noted that in the first case the temperature began to fall following the first dose. This was only two days after an extension of the consolidation from the upper left lobe to the entire left lung. Two more doses were given on successive days and the clinical chart continued to show improvement; the temperature returned to normal and remained there. We did not have serums available to type the organism in this case as we did in subsequent cases, but the organism was identified morphologically and was bile soluble.

The second case began like pneumonia, but consolidation was not detected clinically. This patient had bronchitis. There was a positive blood culture and there were temporary signs of meningitis. An x-ray picture taken with a portable apparatus showed consolidation of the base of the right lung. The sputum contained pus and was streaked with blood. The temperature gradually became lower each day and treatment was instituted very late, but it did produce a change in the form of the temperature curve and brought the disease to an earlier termination.

The third case showed very rapid respirations which remained increased even after the temperature had been normal for some time. This seemed to be due to dry pleurisy which the patient had, and which caused him considerable pain. The rectal temperature returned to 99.6 F. in twenty-four hours following the last treatment. We decided

In consideration of the fact that it is necessary to give the bile salts in dilute solutions to lessen injury to the veins, it would be desirable to use other salts or esters of the bile acids in further experimental work. It may be that other salts or esters of the bile acids could be injected in greater concentrations, with the desired effect of the alkaline salts but without injurious effect on the veins.

SUMMARY

1. Lysis of pneumococci by bile salts (Neufeld's phenomenon) is produced in vitro by extremely weak solutions. In our work, lysis was evident in as dilute a solution as 1:25,000.

2. Neufeld's phenomenon occurs in the presence of serum, but very slowly as compared with its speed in salt solution.

3. Bile salts are approximately five times as lytic for pneumococci as for red blood cells.

4. The exposure of pneumococci to human serum does not interfere with their lysis by bile salts.

5. Bile salts do not interfere in vitro with the antibody (agglutinin) action of specific serums on pneumococci.

6. Intravenous injections of bile salts produce no toxic symptoms. There was no bradycardia and no hemoglobinuria. They have a chologogue action. They produce a slight degree of anemia.

7. Intravenous injections of bile salts, as used in this work, damage the veins in proportion to their concentration, and tend to obliterate them.

8. Icterus in pneumococcus pneumonia is considered to be indicative of a protective mechanism and not of a toxic phenomenon.

9. Bile salts have been used in the treatment for pneumococcus infections previously, but have been used here for the first time in the treatment for pneumonia.

10. Bile salts seem to have a specific effect in terminating pneumococcus pneumonia.

precipitation phenomena occur just the same. These observations *in vitro* could almost certainly be applied to conditions *in vivo*, and especially since clinical results are confirmatory.

From what is known of physiology it would seem that enterotherapy with bile salts would be useless in pneumonia. The salts would be absorbed in the intestine, taken to the liver through the portal system and excreted by the liver into the bile; this is known as the circulation of the bile salts. In view of these facts it would not be expected that the bile salts would enter the general circulation when given by mouth; however, this might be tried.

The damage done to veins by injections of bile salts is considerable. At first it was thought that a 1 per cent solution did not damage the veins; but it was found that even this low concentration eventually caused obliteration in the same manner as the new obliterative chemical treatments for varicose veins. No serious interference with circulation resulted. The deep veins and the superficial ones which remained undamaged were sufficient to carry off the venous blood from the arm. However, in one case (no. 3) the left hand became swollen several days following the treatments and then gradually subsided to normal in about a week. The treated veins had become small and sclerotic and had hard nodules, apparently at the valves.

This effect on the veins at the site of, and for some distance above, the injected point seems to be a serious obstacle to the use of the bile salts in pneumococcus pneumonia. In view of the specific effect which the bile salts seem to have on this type of pneumonia, some method of overcoming this defect is being sought. We have not yet determined the p_H of the bile salt solutions, but we know that they are quite alkaline in reaction, and it may be that an adjustment of the p_H of the solutions would help to remove this damaging effect on the veins. Another promising approach to the problem would be the use of other salts or esters of the bile acids instead of the alkaline salts.

It was thought that perhaps dextrose mixed with the bile salt solutions would help to overcome the lytic effect on endothelium.

The lytic effect on blood cells of a series of bile salt solutions, containing dextrose in each per cent from 1 to 20, was determined. The addition of the dextrose to the bile salt solutions made them many times more lytic for washed blood cells than the controls without dextrose. It was also found that the lytic power was increased proportionately to the concentration of the dextrose.

It is known that cholesterol, ordinarily insoluble in water, is soluble in aqueous solutions of bile salts, and also that cholesterol is an "antilytic" agent. Work is to be undertaken with solutions of bile salts and cholesterol.

Rothberger,⁴ in 1909, injected silver nitrate into the basal ventricular muscle and within five minutes found an increased height of the T wave and within fifteen minutes high take-off or R-T fusion. They did not follow their experiments through as did Smith, but the results are essentially the same. Application of cold by means of ethyl chloride to the same region produced immediate inversion of the T wave. The increased amplitude of the T wave is thus explained by an injury current set up at the time of the infarction augmenting the normal electrical currents, whereas depression of the normal electrical currents, such as follows infarction at a later period or by the immediate application of cold, produces inversion of the T waves.

In table 1 are grouped the cases reported in the literature and my own cases in which electrocardiograms were recorded during the attack or within eight hours afterward. Definite time relationships are often not given; a knowledge of them would be of value in the study of this problem. In only one case besides mine was an electrocardiogram taken before an attack at an interval of less than three weeks (case 6, Willius and Barnes).

During the attack, the records in their case showed more pronounced changes; i. e., a lower T wave in lead I and fusion of the R-T waves in leads II and III. The electrocardiogram in case 7 (Willius and Barnes) taken during the attack showed an inversion of the T waves in leads II and III. This patient, however, had had a previous coronary attack, so that it is impossible to say without subsequent observation whether or not the T wave changes in this record were produced by the attack at that time or by the one a few months before; twenty-four hours later, however, there was inversion of the T waves in all leads. In case 9 (Willius and Barnes) an electrocardiogram taken fifteen minutes after the onset showed no changes, but here again, twenty-four hours later, the T waves were inverted with right bundle branch block.

In case 19 of Parkinson and Bedford an electrocardiogram taken at onset showed upright T waves in all leads. Twenty-four hours later, the T waves in leads II and III were inverted. No record was taken before the attack. In Smith's² case a record taken six hours after onset showed an inverted T wave in lead I, which again is open to the foregoing criticism, as no electrocardiogram was recorded beforehand. Furthermore, there was no appreciable change twenty-four hours after the attack. Nathanson's case was somewhat similar. In Pardee's⁵ case a record taken four hours after the onset of the attack showed character-

4. Eppinger and Rothberger: *Zur Analyse des Elektrokardiogramms*, Wien. klin. Wchnschr. **22**:109, 1909.

5. Pardee, H. E. B.: *An Electrocardiographic Sign of Coronary Artery Obstruction*, Arch. Int. Med. **26**:244 (Aug.) 1920.

THE APPEARANCE TIME OF T WAVE CHANGES IN THE ELECTROCARDIOGRAM FOLLOWING ACUTE CORONARY OCCLUSION

REPORTS OF TWO CASES *

LEWIS M. HURXTHAL, M.D.

BOSTON

The value of the electrocardiogram has frequently been stressed as an aid in the diagnosis of coronary occlusion. Numerous articles have been written on the similarity of the clinical features of coronary occlusion and acute abdominal conditions requiring surgical measures. Herrick,¹ who was one of the first to call attention to coronary thrombosis as a clinical entity, stated the need of more observations to clear up some of the unsolved problems connected with acute obstruction of the coronary artery. He said: "Clinical and prompt decision as to operation for suspected surgical accidents has to be made at times. Detailed reports of such cases would be helpful."

When the emergency of which he spoke arises, of what value is the electrocardiogram and how soon after the occlusion do characteristic changes take place? A search of the literature has revealed comparatively few cases taken shortly after an attack. Obviously, if the electrocardiogram is to be of value in such cases, the time for it to record the characteristic changes should be within the first twenty-four hours.

Experimentally, Smith² found that ligation of the left coronary artery in dogs was followed within from a few minutes to one-half hour by increased amplitude of the T waves. This was later followed by the depression found in human beings following coronary occlusion. Repeated electrocardiograms taken after this showed a gradual return to normal. In human subjects the T wave changes may remain permanent or undergo a return to a more normal state. Parkinson and Bedford³ expressed the belief that the T wave changes are due to an injury current and explain their transient character in dogs and some human beings as being due to an otherwise healthy heart. Eppinger and

* Submitted for publication, March 18, 1930.

* From the Medical Department of the Lahey Clinic.

1. Herrick, J. B.: Some Unsolved Problems Connected with Acute Obstruction of the Coronary Arteries, *Am. Heart J.* **4**:633, 1929.

2. Smith, F. M.: The Ligation of the Coronary Arteries, with Electrocardiographic Study, *Arch. Int. Med.* **22**:8 (July) 1918.

3. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram on Coronary Thrombosis, *Am. Heart J.* **4**:195, 1928.

istic changes. From the history of this case it is probable that the patient had had previous trouble, so that one cannot be absolutely sure of the significance of this record as regards the attack in question. Levine's⁶ case 133 showed upright T waves in all leads five hours after the attack, but twenty-four hours later showed beginning changes.

The other two cases reported by Levine, in which records were taken on the same day of the attack, both showed upright T waves; one exhibited a low T in lead I, later followed by fusion of the R-T in lead II and inversion in T3, and the other immediately showed fusion of R-T waves in all leads. In the case reported by Rothchild, Mann and Oppenheimer, a record taken six and one-half hours after the onset showed fusion of the R-T wave in lead II, which was followed in fourteen days by inversion of the T wave in lead II.

In the cases herein reported an attack developed while the patients were under observation in the hospital. Case 1 is of particular interest in view of the practically normal electrocardiogram taken one hour after onset in spite of an abnormal tracing taken in the hospital six days before. It might be considered analogous to the experimental work of Smith, Eppinger and Rothberger. The one complicating feature, however, was the administration of digitalis in the interim. Had this been a case in which an acute surgical condition in the abdomen had been suspected and had no tracing been taken beforehand, the electrocardiogram would have been decidedly misleading (figs. 1 and 2).

The electrocardiogram in case 2, taken one hour and fifteen minutes after the attack, showed a slight change in the electrical axis, a slight dip in the T wave of lead II and a marked inversion of T3. These can probably be considered significant in the light of subsequent events, although definite inversion of the T wave in lead II was not noted until fifty-six hours after onset. The increased amplitude of the T wave in lead I might have been due to the same mechanism as in case 1, but the release of thyroid secretion following operation might also have caused it.

In summarizing the cases in table 1 taken within six or seven hours of the attack, it is to be noted that eight showed upright T waves in all leads and that six of these were known later to have been followed by inversion of the T wave. Only two of these showed R-T fusion alone as the first sign. There was a history of previous angina pectoris or coronary occlusion in three of these eight cases, but none in four; in one case the history was not known. Five of these cases showed inversion of the T wave in records taken within seven hours. Three of these patients probably had a history of previous pain in the heart, whereas in two the past history was not mentioned.

6. Levine, S. A.: Personal communication to the author.

TABLE 1.—Cases in Which Electrocardiograms Were Taken During the Attack or Within Eight Hours Afterward

Author	Author's Case No.	Previous Attack or Symp- toms	Electrocar- diogram Before Attack	Time After Onset Electrocardiogram Was Taken	Changes in T Wave
Parkinson and Bedford: Am. Heart J. 4: 195, 1928	19	Angina pectoris	0	At onset..... 2 weeks after...	Upright T1, T2, T3 Inverted T2, T3
Willius and Barnes: J. Lab. & Clin. Med. 10: 427, 1924	4	Previous attack Angina pectoris	0	At onset.....	Low, but upright T2, T3
	6		2 days before During attack.	Inverted T2, T3 Inverted T2, T3, lower T1; fusion of R-T in leads 2 and 3
				Day after.....	Inverted T1 (plus previous changes)
	9	0	0	15 min. after attack 24 hours after attack	Upright T1, T2, T3 Inverted T1, T2, T3; right bundle branch block
	7	Previous attack	0	During attack, Next day.....	Inverted T2, T3 Inverted T1, T2, T3
Smith: Arch. Int. Med. 32: 497 (Oct.) 1923	3	Not stated	0	6 hours after onset 24 hours later	Inverted T1 Inverted T1
Nathanson; quoted by Willus and Barnes	..	Not stated	0	4 hours after onset	Inverted T1, T2
Pardee: Arch. Int. Med. 26: 244 (Aug.) 1920	..	Probable angina pectoris	0	4 hours after onset	Inverted T1; fusion of R-T in leads 2 and 3
Levine: Personal communication	61	Angina	0	*Same day..... 24 hours later..	Low, but upright T1 Low T1, fusion of R-T2 and inverted T3
	56	0	0	Same day.....	High take-off of T waves
	133	0	0	? 5 hours after attack ? Next day.....	Upright T1, T2, T3 Beginning depression of T waves
Rothschild, Mann and Oppenheimer: Proc. Soc. Exper. Med. & Biol. 23: 253, 1926	1	Not stated	..	6½ hours.....	High origin, lead II (only one shown)
				6 days.....	Lower origin
				14 days.....	Inversion of T
Hurxthal	1	Nocturnal dyspnea	6 days before 1 hour.....	Inverted T1 Upright T1, T2, T3; low takeoff T1
Hurxthal	2	0	9 days before	Upright T1-T2, inverted T3
				1 hour,	Higher T1, lower T2, deeper T3
				15 min.	Higher T1, deeper T3
				4 hours,	
				5 min.	
				14 hours.....	Same as previous tracing
				33 hours.....	Inverted T2
				16 days	Inverted T2
				27 days.....	Less marked inversion of T2

* It is assumed that records taken the same day were probably taken within eight hours.

was true of case 2 reported here; thus the interpretation of marked inversion of the T waves in lead III probably can be of definite significance only if successive records are made.

So far as can be determined, case 1 herein reported is the first one to be described which closely parallels the experimental work of Smith, Eppinger and Rothberger. It is likely that if more records had been obtained before the attacks in those cases that showed upright T waves, a distinct change in the amplitude of these waves might have been noted. It is hoped that more frequent observations will be made and reported during the first twenty-four hours, especially in those cases in which previous records have been obtained.

One must therefore rely chiefly on clinical observation in doubtful cases to make the diagnosis of acute coronary occlusion if a prompt decision must be made. Serial electrocardiographic observations at hourly intervals, however, may prove helpful.

REPORT OF CASES

CASE 1.—Mrs. F., a housewife, aged 53, had been in good health up to the onset of the present illness, which began gradually with symptoms of weakness, loss of energy and exhaustion. She had been under an emotional strain from the death of her husband, and under a physical strain from lack of sufficient rest during attacks of pneumonia and subsequent influenza during the previous winter. In January her exhaustion required rest in bed. She grew weaker slowly throughout the spring, and in April had an attack of pain in both arms and later in the legs, which her physician thought to be multiple-neuritis. This pain disappeared after about a month, and she had not been bothered with it recently. One month before admission she noticed edema of the ankles and the feet, which persisted. A week or so before admission she noticed nocturnal dyspnea for the first time, and this persisted up to the time of admission. Orthopnea had been present during the same period. She had no cough or precordial pain. Within the previous month a few purpuric lesions appeared without known trauma. Her greatest distress was at night when she had trouble in breathing. She was admitted to the hospital on June 14, 1929.

On physical examination the patient appeared to be well developed but rather pale. The examination of the left eyeground showed marked vascular changes with numerous new hemorrhages and evidence of old ones. The right fundus was not clearly distinguished. Numerous teeth were missing. The thyroid gland was not enlarged. The lungs were clear. The heart was markedly enlarged; the rate was rapid but regular, and there was a systolic murmur at the apex. The abdomen was normal. There was slight pitting edema of the ankles. The blood pressure was 220 systolic and 110 diastolic. A teleoroentgenogram of the heart showed the apex to be opposite the sixth rib anteriorly, 10.6 cm. to the left of the median line. The right border of the heart was 4.2 cm. to the right of the median line. The long diameter of the heart was 15.6 cm.; the diameter of the base was 9.4 cm. The diameter of the great vessels was 6.2 cm. The total width of the chest on the level with the apex of the heart was 23.5 cm. Slight scoliosis of the dorsal spine with the convexity to the right was evident. Examination of the urine revealed a trace of albumin and a specific gravity of 1.010;

Thus, of fourteen patients, six can be considered to have had electrocardiograms that were not diagnostic, two had only high take-offs of T waves ("R-T fusion" "Cove plane T") and six had definitely inverted T waves. In view of the fact that three of the latter patients had an antecedent history of cardiac pain, it is obvious that these records cannot be considered diagnostic of the attack following which they were taken. The Cove plane T is considered by various authors as the first change following coronary occlusion; its value as an early sign is limited in view of the fact that it occurred only four times in these thirteen cases.

It cannot be denied that if T wave changes are found within six or seven hours after the onset of an attack, they are highly suggestive, but

TABLE 2.—Cases in Which Electrocardiograms Were Made About Twenty-Four Hours After the Onset of the Attack

Author	Author's Case No.	Previous Attack or Symptoms	Electrocardiogram Before Attack	Time After Onset Electrocardiogram Was Taken	Changes in T Wave
Parkinson and Bedford	9	0	Next day after attack	Low T
Smith: Arch. Int. Med. 32: 497, 1923	2	Not stated	0	24 hours after	Inverted T1
Wearn: Am. J. M. Sc. 165: 250, 1923	0	Day after.....	Diaphasic T3
Levine: Medicine 8: 246, 1929	15	0	0	Next day.....	Inverted T waves
	11, 20, 33, 140	Angina pectoris	0	Next day.....	Inverted T waves
	10	Angina pectoris	2 years before	Not remarkable
				Day after attack	High origin; low T; inverted T3
Hurxthal	9229	Angina pectoris	0	15 hours.....	Inverted T1; slurring QRS (died)
	368	Indefinite	1 year	18 hours.....	Upright T2 and T3; inverted T1; flat T2

on the other hand they may be entirely absent, may appear to be normal (as in case 1) or may have existed beforehand. Progressive changes will be found in most cases by the end of twenty-four hours, or possibly sooner, or comparisons may be made with records taken beforehand.

In table 2 I have listed my own cases and those reported by others in which records were taken about twenty-four hours after the onset of the attack. Undoubtedly some may have been taken before that time, but, as a rule, the time stated was the next day. It is to be noted that all the cases in the latter group (table 2) showed definite T wave changes. Wearn's case showed only a diaphasic T wave in lead III. Parkinson and Bedford commented on T wave changes in lead III and stated that they believed a marked inversion of T3 highly suggestive of coronary disease. One of their cases showing only this feature was followed up, and subsequent records showed progressive changes. This

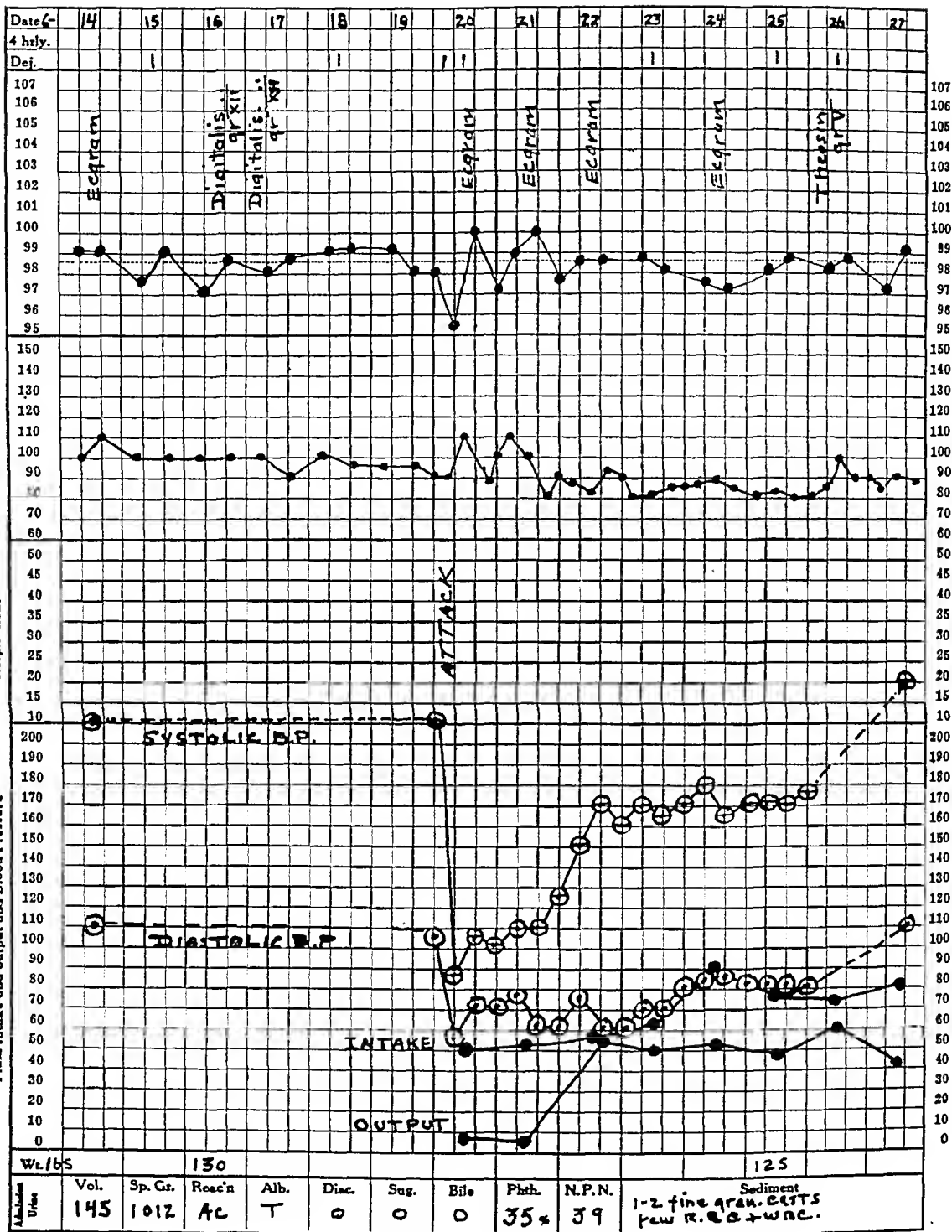


Fig. 2.—Clinical chart in case 1.

microscopic examination revealed one or two fine granular casts and an occasional red cell and white cell to each high power field. The two hour renal test showed a fixation of specific gravity between 1.010 and 1.016. The output of urine during the night was 230 cc.; this showed a specific gravity of 1.016. The two hour renal function phthalein test showed 35 per cent; the nonprotein nitrogen measured 39 mg. per hundred cubic centimeters of blood; the red blood cells numbered 5,010,000, and the white blood cells 13,000; the hemoglobin content was 75 per cent.

On the day of admission an electrocardiogram was taken (fig. 1). The following two days the patient received 24 grains (1.5 Gm.) of digitalis (powdered leaves). After a few days, the edema of the ankles cleared up and the patient thought she slept better at night, with less difficulty in breathing. On the morning of June 20 (six days after admission), the patient was seen as usual; the blood

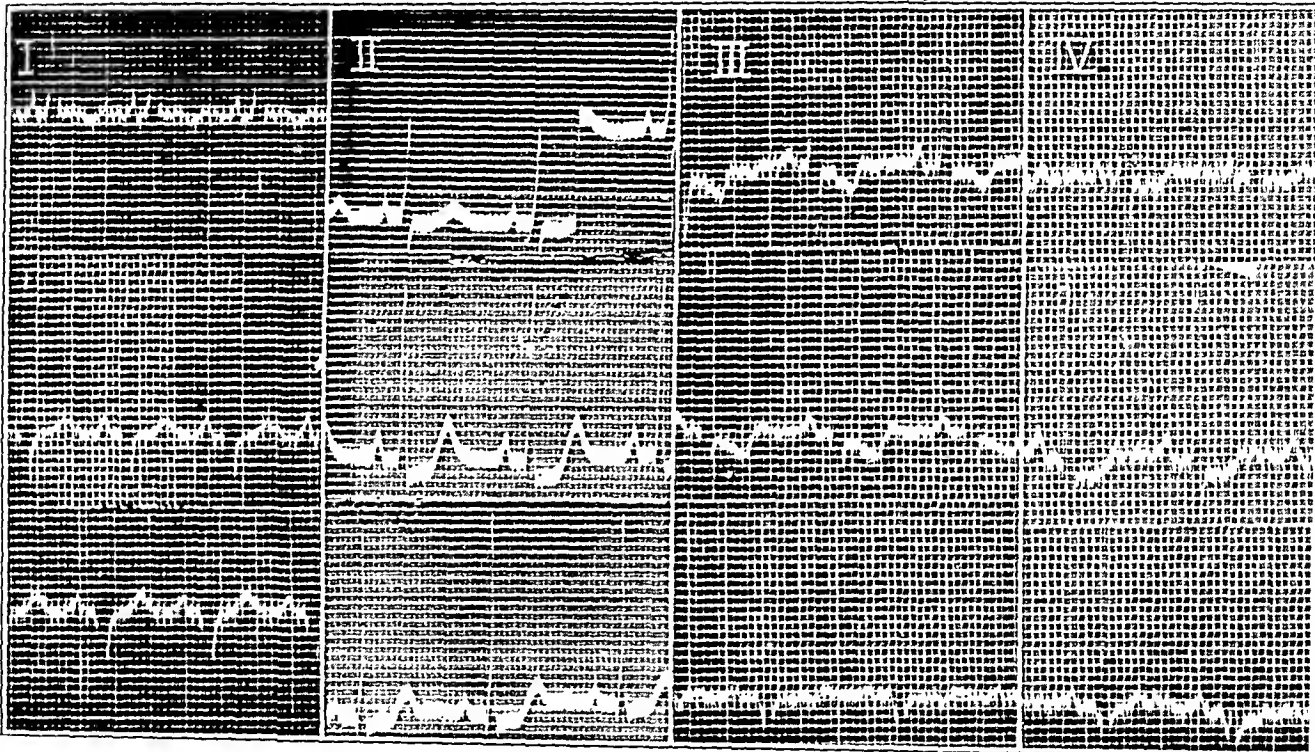


Fig. 1.—Tracings in case 1: I, June 14, 1929 (six days before attack); II, June 20 (one hour after onset); III, June 22, and IV, June 24.

pressure was 210 systolic and 105 diastolic. Shortly afterward, the patient was given a bedpan. While on this she suddenly collapsed and became very weak and short of breath. She complained of no particular pain. Her pulse was very weak, she showed marked pallor, her skin was cold and clammy, and she perspired profusely. Her blood pressure taken immediately after this was 88 systolic and 52 diastolic. A fourth of a grain (0.016 Gm.) of morphine was given hypodermically. Just before the injection the patient was conscious of a little pain over the region of the heart.

After the hypodermic injection an electrocardiogram was made, which is shown in figure 1 (II). The patient's condition gradually improved, but during the next two days she had an almost complete suppression of urine, with the recurrence of edema, slight tenderness of the liver and pitting edema of the sacrum. Subsequently the condition improved, and the blood pressure gradually rose to its

genogram of the heart gave the following measurements: The apex was opposite the seventh rib anteriorly, 12.5 cm. to the left of the median line. The right border was 5 cm. to the right of the median line. The diameter of the lung was 17.8 cm., and the diameter of the base, 9.2 cm. The diameter of the great vessels was 7.9 cm. The width of the chest at the level of the apex was 26.8 cm.

Examination of the urine showed a specific gravity which ranged from 1.020 to 1.030. There was a light precipitate of albumin at all examinations. The sediment was negative. The phthalein excretion was 40 per cent in two hours and ten minutes. On several occasions there was from 0.1 to 0.3 per cent sugar in the urine. The fasting blood sugar was 0.1 per cent. The nonprotein nitrogen was 32 mg. per hundred cubic centimeters of blood. The Wassermann reaction was negative.

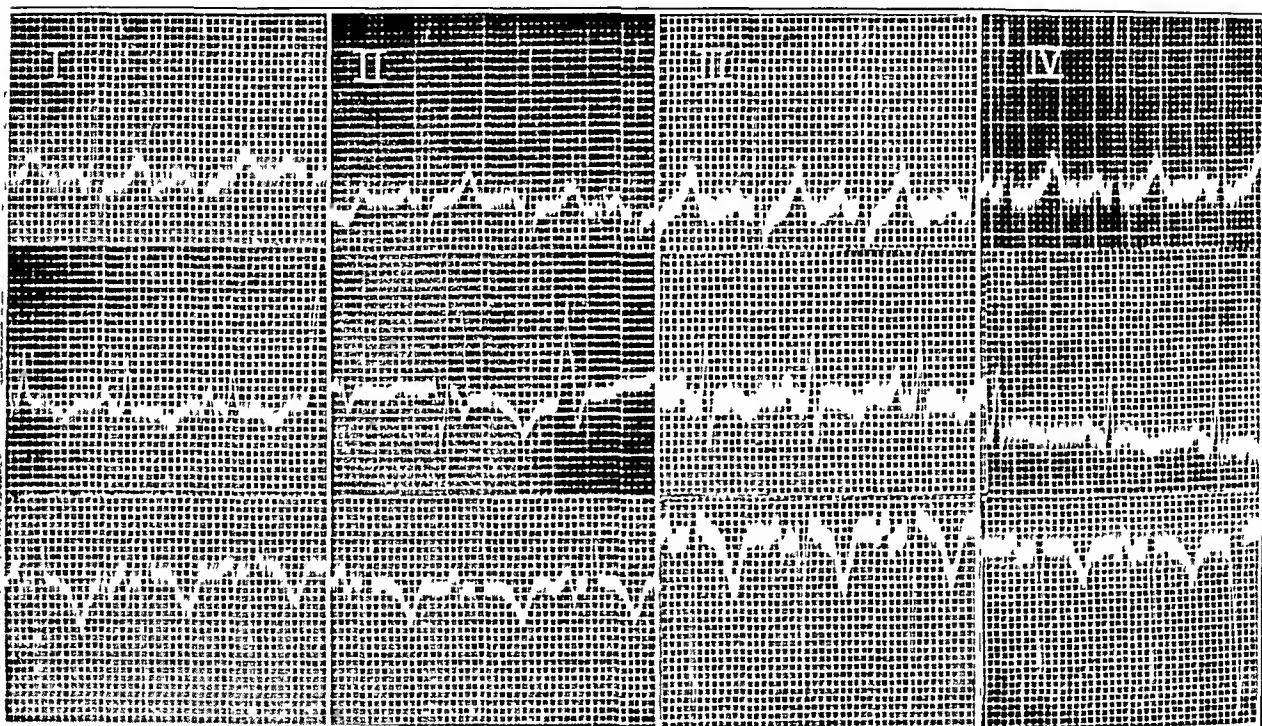


Fig. 4.—Further tracings in case 2: I, Dec. 6, 1929; II, December 7; III, December 20, and IV, December 31.

The patient was operated on, Nov. 29, 1929. The left lobe of the thyroid was found to be about eight times the normal size, with a much enlarged isthmus. The trachea was deviated markedly to the right. A left subtotal thyroidectomy was performed. The patient went through the operation without incident, and did well until December 5. Following an enema and the use of the bedpan, the patient was seized with marked dyspnea and orthopnea, and profuse sweating. No pain was experienced. The blood pressure was 120 systolic and 95 diastolic and the heart rate was rapid with a gallop rhythm and occasional extrasystoles. An electrocardiogram was taken an hour and fifteen minutes later (figure 3 [II]). The patient was given morphine, and electrocardiograms were taken on subsequent dates (figs. 3 and 4). The patient recovered satisfactorily and was transferred to her home three weeks after the date of the attack (fig. 5).

previous level; when she was discharged from the hospital, approximately one month later, her blood pressure was 220 systolic and 105 diastolic (fig. 2).

She progressed fairly well at home until about three months later, when she experienced another similar attack from which she recovered. When last seen, she was up and about, but was almost completely blind.

CASE 2.—A single woman, aged 59, came to the clinic on Nov. 22, 1929. Her past history was essentially unimportant except for scarlet fever in childhood. She complained chiefly of shortness of breath and nervousness for the past year. For the last few months she had been taking medicine for high blood pressure.

Examination showed a well developed woman with good color. Physical examination revealed the absence of teeth. The eyegrounds showed slight compression of the veins and marked tortuosity of the vessels. The blood pressure

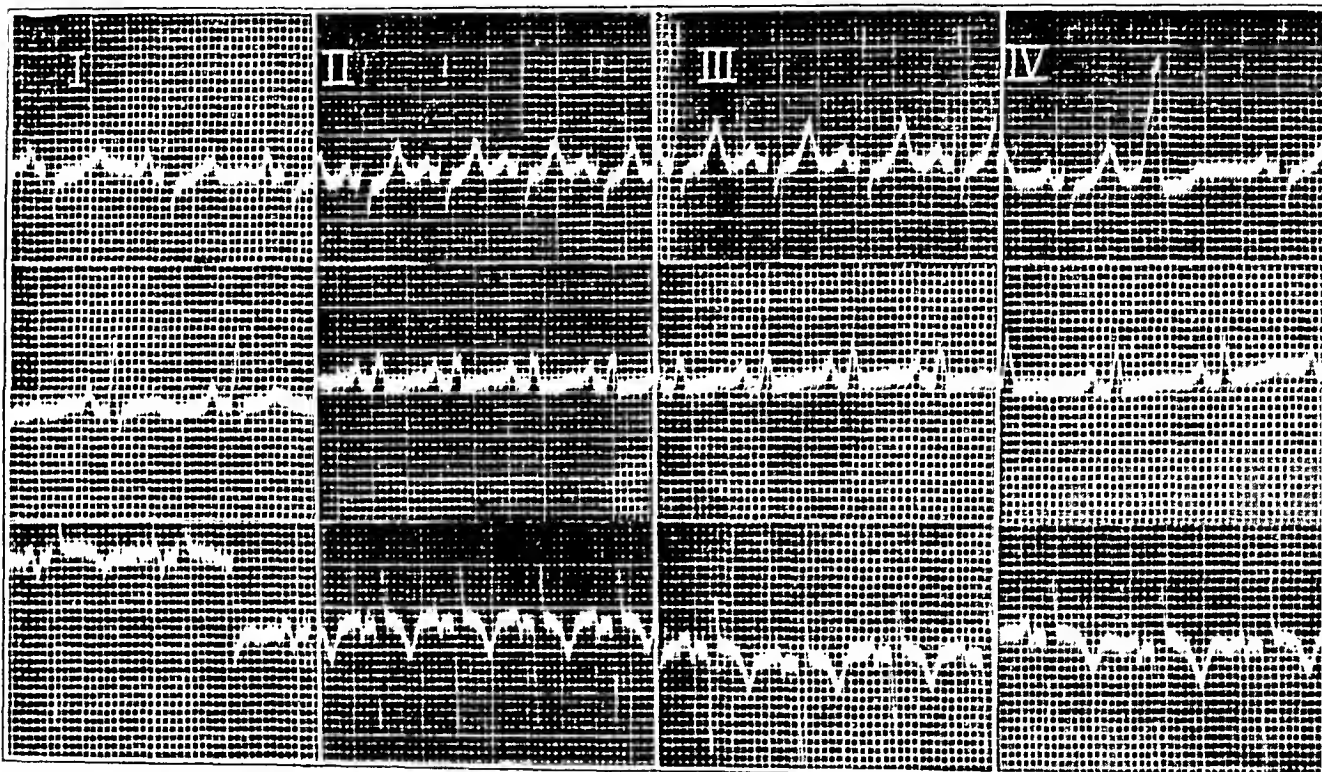


Fig. 3.—Tracings in case 2: I, Nov. 25, 1929 (before onset); II, December 4 (one hour and fifteen minutes after onset); III, four hours and five minutes after onset, and IV, December 5 (fourteen hours after onset).

was 155 systolic and 100 diastolic. The skin was warm, and there was a slight tremor. The heart was moderately enlarged, showing numerous extrasystoles. The lungs were clear; the abdomen showed nothing abnormal; the legs revealed moderate-sized varicose veins. The patient was slightly deaf in both ears. The thyroid showed a nodular enlargement on the left side, extending below the clavicle. Roentgen examination of the trachea showed it to be markedly deviated to the right.

The patient was sent to the hospital for observation and decision as to operation. The electrocardiogram taken at that time is shown in figure 3. The basal metabolic rate was +21 per cent; the pulse rate, 70; the weight, 154 pounds (69.8 Kg.), and the blood pressure, 170 systolic and 90 diastolic. A teleroent-

She was seen again four weeks after the attack, at which time her blood pressure was 170 systolic and 110 diastolic. Extrasystoles were present. The patient was having no trouble, although her activity had been markedly restricted. The electrocardiogram taken at this time is shown in figure 4.

SUMMARY AND CONCLUSIONS

1. The value of the electrocardiogram in the diagnosis of coronary occlusion has been repeatedly emphasized.

2. Experimental work cited shows that increased amplitude of the T wave follows ligation or injury to the muscles supplied by a coronary artery; cooling causes depression of the T wave.

3. Case reports from the literature have been reviewed; twelve cases were found in which records were taken within eight hours after an attack of coronary thrombosis. Only one patient had a record taken within three weeks before an attack.

4. Two cases are reported in which records were obtained before and after attacks. Case 1 showed upright T waves in all leads one hour after the onset of the attack, later followed by depression, whereas the record six days before the attack showed an inverted T wave in lead I. Case 2 showed a distinct but not diagnostic change one hour and fifteen minutes after onset.

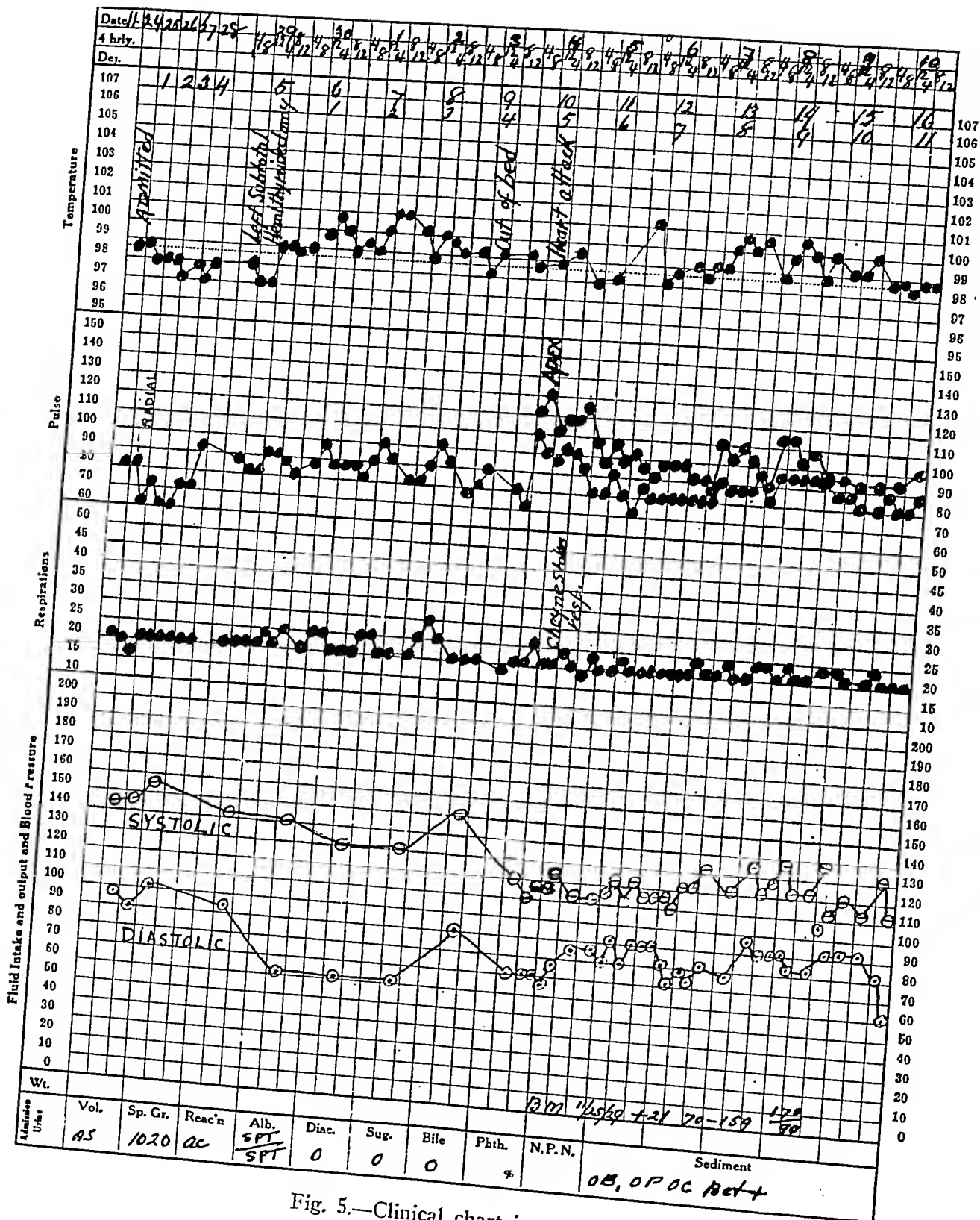
5. Eight cases in the literature showed upright T waves within eight hours after onset. Only four showed R-T fusion, and six showed inverted T waves.

6. Seventeen cases showed definite T wave changes taken the day after the attack.

7. Single tracings immediately following acute coronary occlusion may appear normal, or if abnormal are of little value unless previous records have been taken or later records are obtained.

8. At present, one must rely on clinical diagnosis rather than on the electrocardiogram in an emergency in which surgical measures are considered.

9. It is suggested that electrocardiographic observations be made at more frequent intervals following acute coronary occlusion. Such observations may prove of distinct value in diagnosis.



Since these observations were made, Carlson and one of us (O. H. W.)¹ have tried to establish a comparison of the peristaltic activity of the various segments of the bowel in intestinal obstruction. By passing a small inflated balloon into the intestine distal to the obstruction a better quantitative estimate may be obtained of the ability of this segment to contract in dogs with intestinal obstruction. In the dogs in which the peristaltic activity was measured in this manner, it was soon apparent that definite peristaltic contractions could be elicited. Comparison with the peristaltic activity of the normal dog's intestine demonstrated a quantitative reaction of approximately the same charac-

Expulsion of Enemas in Intestinal Obstruction

Dog	Type of Obstruction	Length of Survival, Days	Number of Enemas	Number of Evacuations Containing Gas and Fees	Barium Sulphate Injected	Condition of Distal Bowel Post Mortem	Approximate Number of Hours Before Barium Sulphate Appeared in Stool
1	High complete obstruction; inversion method with enterostomy	4	1	1	+	Normal	6
2	High complete obstruction; inversion method with enterostomy	7	4	3	+	Spastic	6
3	High complete obstruction; inversion method with enterostomy	6	4	3	+	Spastic	24
4	High complete obstruction; inversion method with enterostomy	5	3	3	+	Semisplastic	5
5	Complete low obstruction; no enterostomy	5	4	4	0	Flaccid	..
6	Low strangulation obstruction with Witzel enterostomy	1	2	2	+	Semisplastic	..
7	High strangulation obstruction with Witzel enterostomy	1	2	2	+
8	Low partial obstruction with Witzel enterostomy	..	3	3	+
9	Low partial obstruction with Witzel enterostomy	2	2	2	+	Normal	6

ter. The obstructed loop, however, exhibits greater contractile power than either the normal intestine or the segment distal to the point of obstruction. The latter segment reacts to subcutaneous injections of pilocarpine hydrochloride or solution of pituitary much as does the normal segment; the reaction of the obstructed segment to similar drugs is much more intense, however.

During the time that these experimental observations have been carried on, we have had adequate opportunity to observe similar behavior in the segment of bowel beyond the obstruction in the human being.

1. Carlson, H. A., and Wangenstein, O. H.: Motor Activity of the Distal Bowel in Intestinal Obstruction: Comparison with the Obstructed and Normal, Proc. Soc. Exper. Med. & Biol. **27**:676-681, 1930.

EVALUATION OF THE EXPULSION OF ENEMAS AS A CRITERION OF INTESTINAL OBSTRUCTION*

OWEN H. WANGENSTEEN, M.D.

AND

REINHOLD O. GOEHL, B.S.

MINNEAPOLIS

The persistently poor results obtained by surgeons in acute intestinal obstruction are in a large measure due to delay in diagnosis. Clinicians have been disposed to place a good deal of reliance on the expulsion of an enema as evidence militating against the presence of mechanical obstruction in the bowel, and there exists a general unwillingness to accept the diagnosis of acute obstruction of the intestine as long as enemas continue to be returned with the expulsion of gas and feces.

In this study an attempt has been made to evaluate the significance of the expulsion of enemas as a criterion of intestinal obstruction.

In a series of nine dogs, obstructions of varying types were established, and Noble's enemas were subsequently administered. In four animals a high jejunal complete obstruction was established by severing the bowel and inverting the proximal end; the distal end was brought up and anchored to the skin. In another dog a low complete ileal obstruction was established, and in two others partial obstructions were made by ligating the bowel with gauze. In two other animals a strangulation obstruction was made by tying off with gauze about 3 feet (0.9 meter) of the intestine together with its mesentery.

In the partial and strangulation types of obstruction a urethral catheter was placed into the distal bowel by the Witzel enterostomy technic. As the accompanying table indicates, dogs in which complete obstructions have been established, as well as animals having partial obstructions or strangulation obstructions, regularly expel enemas on their administration.

Barium sulphate was injected through the catheter into the distal loop of a number of animals, and the transit of barium through the bowel was followed by roentgenograms. The rate of transit of barium through the distal bowel is apparent from the table. In most cases the time of transit was normal; in a few cases it was delayed. In a few of the x-ray films a spastic contraction of portions of the distal loop was noted.

* Submitted for publication, April 12, 1930.

* From the Department of Surgery, University of Minnesota.

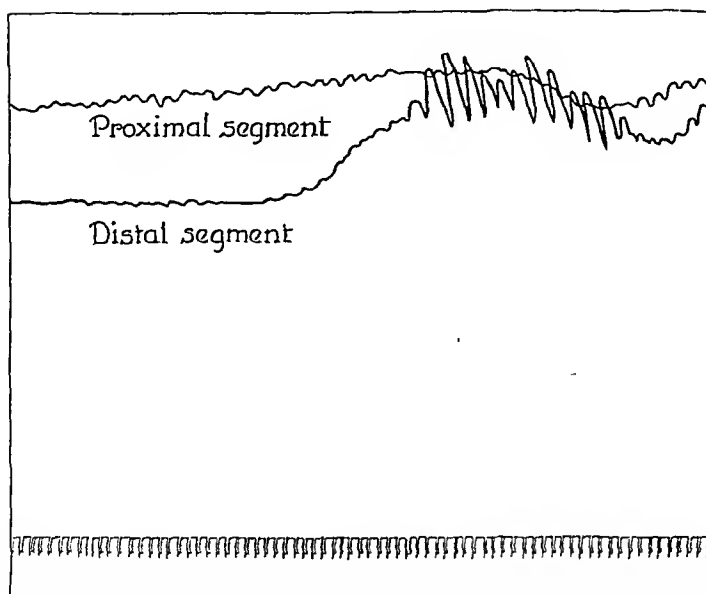


Fig. 2.—Drawing from a tracing obtained by placing rubber balloons into the intestine. Five hours previously a severed intestinal obstruction had been established. The distal segment appears even more active than the proximal.

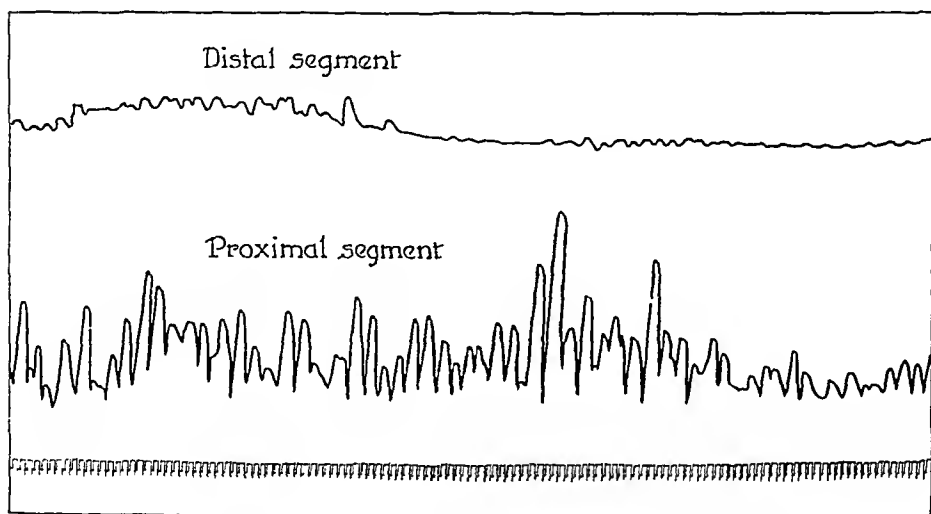


Fig. 3.—Similar tracing made from a dog with severed intestinal obstruction of seven days. The peristaltic activity of the obstructed bowel is unusually great for an obstruction of that duration.

patient has acute intestinal obstruction. In all the disasters or catastrophes of an acute nature to which the abdomen is heir, with the single exception of intestinal obstruction, definite local observations that at least suggest the necessity for surgical intervention are present. Local tenderness, rigidity or muscle spasm is absent. These facts may be presented in extenuation of the late recognition of most instances of acute obstruction of the bowel. At the same time the occurrence of intermittent, crampy, colicky, abdominal pain followed by nausea and reflex vomiting without local physical observations should immediately suggest the possibility of intestinal obstruction.

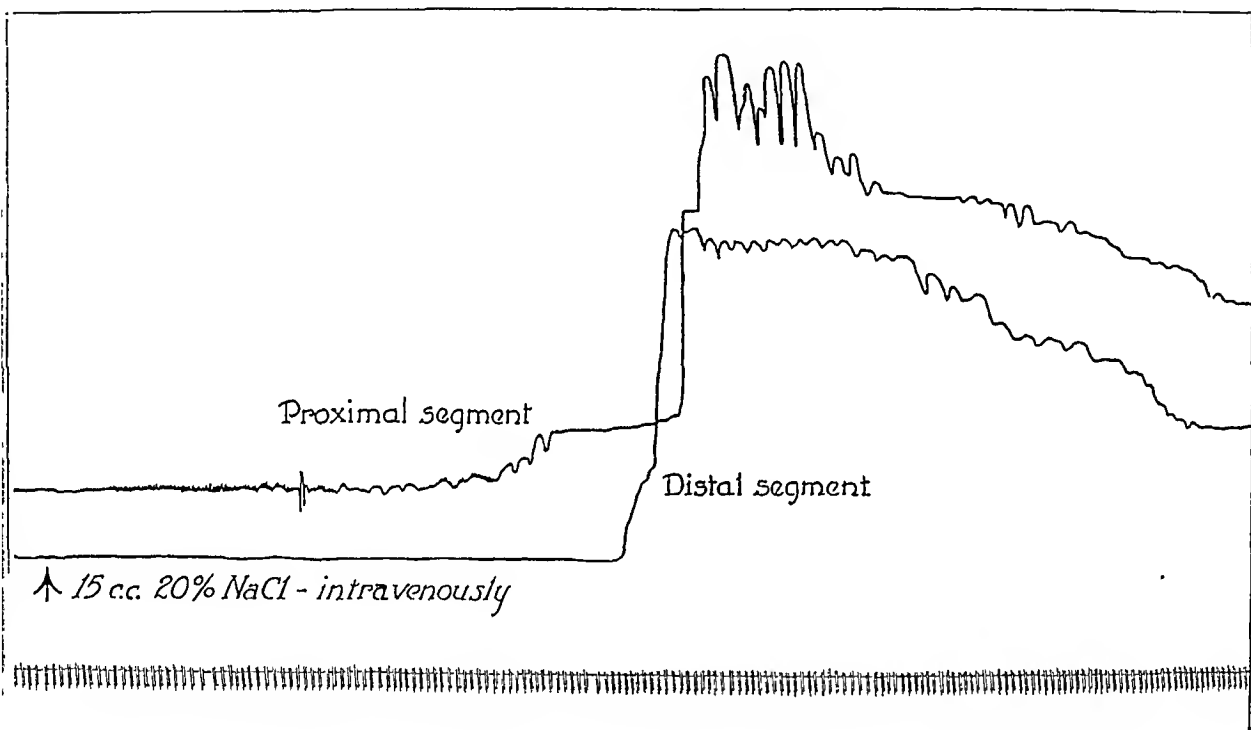


Fig. 5.—The effect of the intravenous injection of hypertonic solution of sodium chloride. A similar response is obtained from the bowel distal to the obstruction as is observed in the obstructed intestine.

Visible peristalsis, though observed in almost every instance of subacute or chronic intestinal obstruction, is rarely seen in acute obstruction. The auscultation of the abdomen, however, gives evidence of real value. In the absence of visible peristalsis, loud peristaltic rushes like the bubbling sound produced by pouring water out of a bottle may be heard with the stethoscope when a mechanical obstruction exists. A dilated intestine in which considerable fluid and air are present is necessary to elicit these bubbling sounds. Near the point of intestinal occlusion these intestinal noises may attain explosive force. Frequently a metallic tinkle may be heard, a sign of conclusive significance for the

obstruction of the bowel exists. All of these phenomena may be observed at some time during the course of intestinal obstruction, but their importance as measures of diagnostic value must be properly appraised. In his nonpareil text on the principles and practice of medicine, the late Sir William Osler³ says, "The sequence of gastric, bilious, and finally stercoraceous vomiting is perhaps the most important diagnostic feature of acute obstruction." That this in part is true must be freely conceded, but it is decidedly unsafe to await confirmation



Fig. 7.—The same dog after ten hours.

of this succession of events. Similarly, absolute constipation, meteorism and collapse may establish the diagnosis, but at a time when the patient is beyond hope and remedy. Regurgitant vomiting and abdominal distention are rather to be considered as heralds of death than as symptoms of acute intestinal obstruction.

3. Osler, William: *Principles and Practice of Medicine*, ed. 8, New York, D. Appleton & Company, 1918, p. 542.

surroundings. The air that is swallowed during the ingestion of food remains for a time in the stomach as the large gaseous "stomach bubble," and in the digestive processes that continue in the small intestine, carbon dioxide largely is formed and is absorbed almost as readily. Normally, protein putrefaction begins in the large intestine; as a product of this bacterial activity, nitrogen, hydrogen, methane and hydrogen sulphide are formed, which are absorbed much less readily than carbon dioxide. At the same time, it is to be remembered that the transit of food through



Fig. 9—Roentgenogram made in standing posture showing "fluid mirrors." The patient had had obstructive symptoms of twelve hours' duration. No clinical distention, loud borborygmi and a metallic tinkle were the only physical observations.

the small intestine is rapid. In the stomach and in the colon progress of the content of the digestive tract is considerably slower.

The demonstration of gas in the small intestine on the x-ray film is therefore decidedly abnormal and is indicative of the presence of a mechanism interfering with the normal rate of transit through the small intestine. It is to be remembered, however, that this mechanism

Long before clinical distention is apparent, an x-ray film of the abdomen will reveal intestinal dilatation. Satisfactory roentgen demonstration of gaseous shadows in the small intestine in a patient who has intermittent crampy pain without local physical observations other than loud borborygmi would lend tenable and substantial support to the impression that an obstruction exists.

Normally, gas is visible on the x-ray film in the stomach and colon, especially at the hepatic and splenic flexures, but cannot be visualized

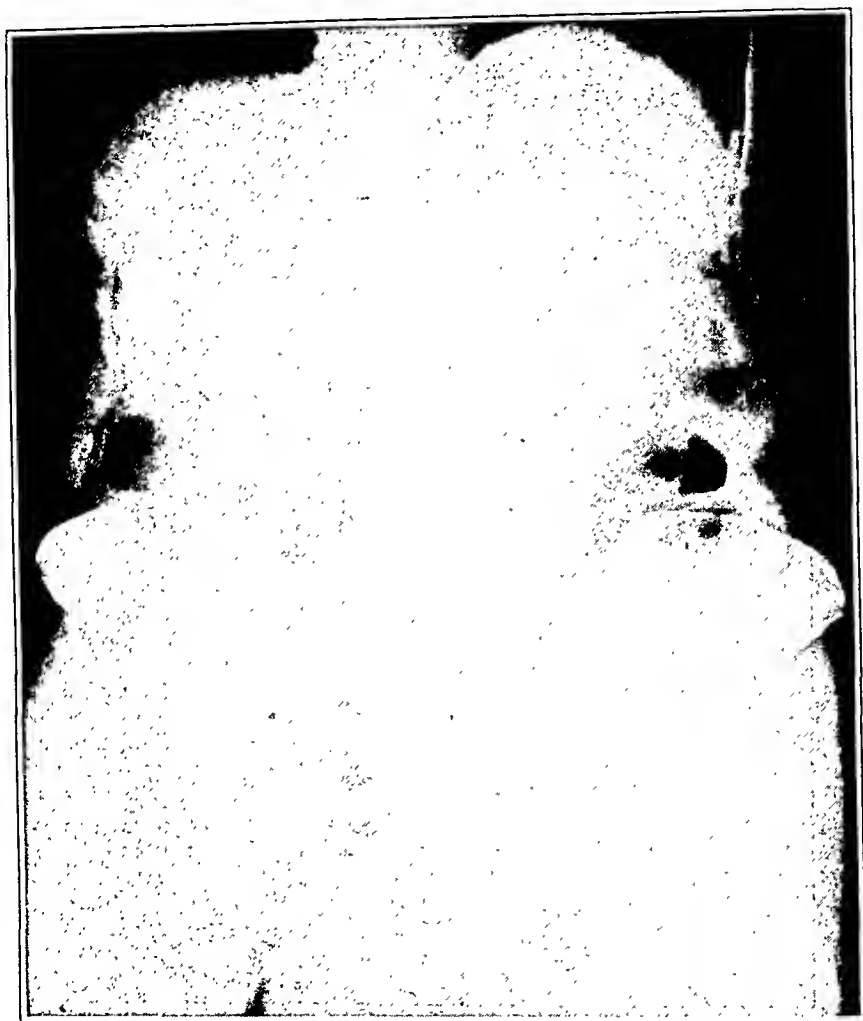


Fig. 8.—Roentgenogram of the abdomen of a woman who had complained of intermittent colicky pain for seven hours. There is gaseous distention of a small loop of small intestine on the left side of the abdomen. Loud intestinal noises on auscultation were the only physical observation. An adhesive band was found at operation.

through the length of the small intestine. That gas is present in the small intestine is well known. Every surgeon is familiar with the small bubbles of intestinal fluid and air that escape when the normal intestine is incised. The intimate intermixture of gas and fluid probably precludes the gas being distinguished normally from the immediate

PRIMARY CARCINOMA OF THE LUNGS WITH METASTASES TO THE CENTRAL NERVOUS SYSTEM *

CHARLES DAVISON, M.D.

AND

WILLIAM A. HORWITZ, M.D.

NEW YORK

Metastases of primary carcinoma of the lung to the central nervous system and other organs are not infrequent. Simpson,¹ in a collection of 139 cases of patients who were admitted to the London Hospital between 1907 and 1925, and in whom primary carcinoma of the lung was found post mortem, stated that metastases were noted during life in about 25 per cent of the cases. Adler,² in a collection of 327 cases, found only 33 cases in which there were no metastases. Frequently the metastases constitute the first sign of the disease, producing symptoms and signs in the organ involved, without any evidence of the primary site of the growth, thus leading to errors in diagnosis. Simpson,¹ in the analysis of his cases, found 66 in which the condition was diagnosed incorrectly, and of these 18 were placed in the domain of diseases of the central nervous system (13 in the cerebral group and 5 in the spinal group). Dosquet,³ in 105 cases of carcinoma of the lungs found involvement of the central nervous system in 31.4 per cent. Fried,⁴ in a collection of 10 cases, found metastases to the central nervous system in 4, and in 1 of the cases the signs and symptoms led to a clinical diagnosis of alcoholic psychosis. The condition in only 3 of the 10 cases reported was diagnosed clinically as primary pulmonary carcinoma. Parker⁵ reported 4 cases of primary carcinoma of the lung with invasion of the brain, meninges, spine and nerve roots, in which the pulmonary signs were few and the involvement of the nervous system was the most striking feature.

*Submitted for publication, March 5, 1930.

*From the Neuropathology Laboratory, Montefiore Hospital.

1. Simpson, S. L.: Primary Carcinoma of the Lung, *Quart. J. Med.* **87**:413 (April) 1929.

2. Adler, I.: Primary Malignant Growth of the Lungs and Bronchi, New York, Longmans, Green & Company, 1912.

3. Dosquet, quoted by Parker (footnote 5).

4. Fried, B. M.: Primary Carcinoma of the Lungs, *Arch. Int. Med.* **35**:1 (Jan.) 1925.

5. Parker, H. L.: Involvement of the Central Nervous System Secondary to Primary Carcinoma of the Lungs, *Arch. Neurol. & Psychiat.* **17**:198 (Feb.) 1927.

Neurologic Examination.—The pupils were irregular and reacted slowly to light; the fundi revealed optic atrophy. There was a slight right facial palsy. The patient was in the hospital only four days when he died suddenly on March 25, 1922. A diagnosis of neoplasm involving the left lung, the wall of the chest and the second rib was made.

TABLE 1.—*Observations on Cases of Primary Carcinoma of the Lungs with Involvement of the Central Nervous System by Metastases in Which the Brains and Spinal Cords Were Removed*

Case, Sex, Age	Duration of Illness, Years	Onset of		Clinical Diagnosis	Clinical Neurologic Signs Due to Metastases	Observations at Autopsy	Involvement of Central Nervous System, Single or Multiple	Histogenesis of Tumor
		Pulmonary Signs	Neurologic Signs					
1 M 70	?	Sudden	Sudden	Carcinoma of lungs	Optic atrophy facial palsy	Carcinoma of lungs with metastases to brain and various organs	Single	Bronchial
2 M 64	9	Gradual	Sudden	Carcinoma of lungs with cerebral metastases	Aphasia; left hemiplegia	Carcinoma of lungs with metastases to brain and various organs	Single	Bronchial
3 F 34	6	Gradual	Sudden	Carcinoma of lungs; chronic pulmonary tuberculosis; tuberculoma or tuberculous meningitis	Papilledema; Kernig's sign; exaggerated reflexes	Carcinoma of lungs with metastases to brain and various organs	Multiple	Bronchial
4 F 40	1½	Sudden	Sudden	Gumma; broncho-pneumonia; dementia paralytica; possibility of cerebral neoplasm	Argyll-Robertson pupils; choked disk; mental picture of dementia paralytica	Carcinoma of lungs with metastases to lymph nodes of the hilus and brain	Single	Bronchial
5 F 58	1	Sudden	Sudden	Chronic fibroid phthisis; generalized arteriosclerosis	Headache; tinnitus	Carcinoma of lungs with metastases to brain and various organs	Multiple	Bronchial
6 M 50	1	Sudden	Sudden	Carcinoma of lungs	Headache; dizziness	Carcinoma of lungs with metastases to brain and various organs	Multiple	Bronchial
7 M 61	2	Gradual	Sudden	Chronic pulmonary tuberculosis; compression of spinal cord	Signs of spinal cord tumor; level lesion	Carcinoma of lungs with metastases to various organs and vertebral column	Single	Bronchial

Laboratory Data.—A roentgenogram showed a dense circumscribed homogeneous shadow occupying nearly the entire upper lobe of the left lung. The ninth rib on the right side showed a partial destruction of its posterior portion. The Wassermann test of the blood was negative.

Anatomic Diagnosis.—The condition was diagnosed neoplasm of the left lung with extension through the first intercostal space and partial erosion of the second rib with metastases to the ribs, suprarenal gland and brain; generalized arteriosclerosis, and terminal bronchopneumonia.

Metastases to the brain are considered to take place by two routes, (1) through the blood stream, the tumor cells being carried by the pulmonary veins to the left side of the heart and thence by the general circulation to the central nervous system, and (2) by direct extension through the cervical lymph glands and the lymphatic spaces of the neck. According to Hassin,⁶ the tumor cells may be carried from the lymph glands of the neck by a backward flow of the lymph through the perineural sheath to the subdural and subarachnoid spaces, and then to the cerebral meninges. The first method of invasion is the more common.

A series of cases of primary carcinoma of the lungs with involvement of the central nervous system presenting some interesting features induced us to investigate this problem.

MATERIAL

This work covers the investigation of 109 cases with a clinical diagnosis of primary carcinoma of the lung at the Montefiore Hospital since 1922. Of these, 61 cases came to autopsy, and the condition was proved to be primary carcinoma of the lungs. Twelve of the total number of cases presented involvement of the central nervous system, chiefly in the form of cerebral and cerebellar metastases, with only 3 cases showing pure metastases to the spinal cord in the form of transverse myelitis. The brains and spinal cords were obtained in only 7 of the 12 cases. The cases showing involvement of the central nervous system were divided in two groups: (1) those of primary carcinoma of the lungs with involvement of the central nervous system by metastases in which the brains and spinal cords were removed (table 1) and (2) those of primary carcinoma of the lungs showing clinically involvement of the nervous system in which the brains and spinal cords were not obtained at autopsy (table 2).

REPORT OF CASES

Group 1.—Cases of Primary Carcinoma of the Lungs with Involvement of the Central Nervous System by Metastases in Which the Brains and Spinal Cords Were Removed (Table 1).

CASE 1.—History.—M. C., a man, aged 70, a presser, was admitted to the Montefiore Hospital on March 20, 1922. On account of the patient's mental condition, a satisfactory history could not be obtained.

Physical Examination.—Examination revealed a pale, anemic, emaciated man who presented a palpable and painful mass in the left infraclavicular fossa. The chest showed dullness of both apexes posteriorly, flatness of the left infraclavicular fossa and bronchial breathing. The heart and the rest of the organs were normal.

6. Hassin, G. B.: Histopathology of Carcinoma of the Cerebral Meninges, Arch. Neurol. & Psychiat. 1:705 (June) 1919.

CASE 2.—*History*.—A. L., a man, aged 64, a salesman, was admitted to the hospital on Nov. 22, 1926. About September, 1923, the patient complained of pain in both flanks and loss in weight. In July, 1926, he sustained a fall and bruised his head; this was followed by a paralysis of the right arm. Six days later, he fell again. A left facial palsy, stuttering and incontinence of both sphincters developed. He fell out of bed and was semiconscious for two weeks, following which left hemiplegia and marked aphasia developed. For the nine

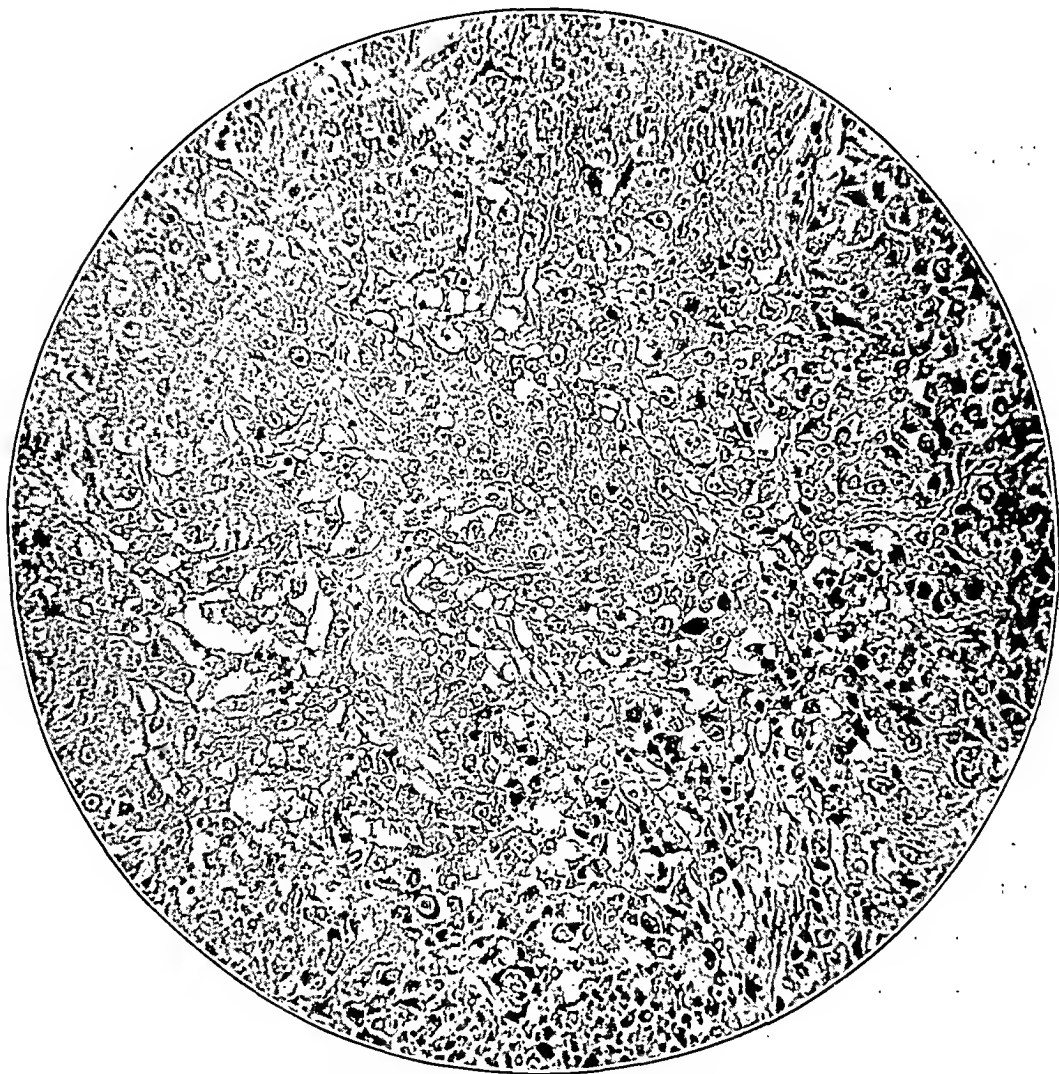


Fig. 1.—Metastatic carcinoma simplex, bronchial in origin, showing pale cells with large, vesicular nuclei and others with strikingly pyknotic nuclei; hematoxylin and eosin stain; $\times 300$.

years before admission he had coughed, bringing up considerable thick, yellowish sputum.

Physical Examination.—Examination revealed a markedly emaciated, cachectic man with the mouth drawn to the left. The right side of the chest expanded poorly. There was an area of dullness on the right side anteriorly from the third to the fifth ribs and posteriorly from the fifth interspace to the angle

Autopsy Observation on the Brain.—The brain showed a slight edema over the parietal region. A large tumor nodule 3 cm. in diameter was found immediately underneath the occipital angle, breaking through the cortex on the left side. The vessels at the base were slightly thickened. On sectioning the brain, a tumor mass was found located in the left parieto-occipital area.

Microscopic Report on the Metastatic Nodule to the Brain.—The tumor cells, squamous in type, were large, deeply staining, polygonal, round and flattened, containing distinct round vesicular nuclei. In places, the cells were pale with large nuclei and strikingly prominent nucleoli (fig. 1). For the most part a thin connective tissue stroma acted as the supporting framework for individual and several layers of cells. In places there was a tendency to alveolar formations,

TABLE 2.—*Observations on Cases of Primary Carcinoma of the Lungs Showing Clinical Involvement of the Nervous System by Metastasis in Which the Brains and Spinal Cords Were Not Obtained at Autopsy*

Case, Sex, Age	Dura- tion of Illness, Months	Onset of		Clinical Diagnosis	Clinical Neurologic Signs Due to Metastases	Observations at Autopsy	Comment
		Pulmo- nary signs	Neuro- logic signs				
1 M 48	2	Sudden	Sudden	Carcinoma of lungs	Babinski sign; stupor; incontinence	No postmor- tem exami- nation	Brain and cord not removed
2 M 46	24	Sudden	Sudden	Carcinoma of lungs with metastases to the spine	Horner's syn- drome; lesion at level of D-4-5	No postmor- tem exami- nation	Brain and cord not removed
3 M 47	13	Sudden	Sudden	Carcinoma of lungs; pulmonary tuberculosis	Multiple neurologic signs, chiefly of the bulb	No postmor- tem exami- nation; primary carcinoma of the lungs	Brain and cord not removed; patient died at home
4 F 56	12	Gradual	Gradual	Carcinoma of lungs; chronic encephalitis; cerebral metastasis	Chronic encephalitis; left hemi- plegia; aphasia; convulsions	Carcinoma of lungs	Brain and cord not removed
5 M 53	11	Sudden	Sudden	Carcinoma of lungs with metastasis to spine	Transverse lesion at D-8	Carcinoma of lungs	Brain and cord not removed

and in the necrotic areas tumor cells were found invading the walls of the blood vessels (fig. 2).

Microscopic Diagnosis.—The microscopic diagnosis was carcinoma simplex (bronchial in origin).

Comment.—The short stay of this patient in the hospital and the poor history obtained owing to the patient's mental condition rendered this case unsatisfactory for diagnosis. The interesting features were the palpable masses in the infraclavicular fossa and the solitary tumor nodule invading the brain tissue. The involvement of the glands of the neck and the solitary metastatic nodule to the brain are in favor of a direct extension of the mass from the cervical lymph glands and the lymphatic spaces of the neck by a backward flow of the lymph.

sharply delineated, but along its external aspect there were a few infiltrating bands. Roentgenograms of the lumbar and dorsal spine were negative. Examination was suggestive of a neoplasm.

The patient died on Dec. 17, 1926.

Diagnosis—The clinical diagnosis was carcinoma of the lung with metastases and left internal capsular hemorrhage due to metastases. The anatomic diagnosis was carcinoma of the left lung with metastases to the left suprarenal gland and brain with extension into the pancreas and left kidney; fibroma of the dura, generalized arteriosclerosis and terminal vegetative endocarditis.



Fig. 3.—Metastatic nodule to the frontal area.

Autopsy Observations on the Brain.—The gyri were swollen and flattened, and the left hemisphere was enlarged. On cutting the brain vertically, a tumor-like mass was found in the left hemisphere extending frontally into the pre-central gyrus (fig. 3) and caudally into the interior third of the middle parietal gyrus. The tumor was reddish. The rest of the central nervous system revealed no abnormalities.

The microscopic examination of the metastatic nodule of the brain showed the same histologic features as the primary tumor with extensive degeneration of the nervous tissue (fig 4). A descending degeneration of the left pyramidal tract was found in the pons, medulla oblongata and the lower cervical segments of the cord. This tumor presented a single cerebral metastasis.

of the scapula, with tubular breathing which was heard over this entire area. The left lung, as well as the rest of the organs, was negative.

Neurologic Examination.—The pupils were the size of a pin-point and reacted slightly to light. There was a right lower facial palsy. The tongue deviated to the right. All extremities were flaccid, with marked atrophy of the muscles of the lower extremities. Sensation was unsatisfactory, as the patient cooperated poorly. The reflexes of the upper extremities were normal. Both

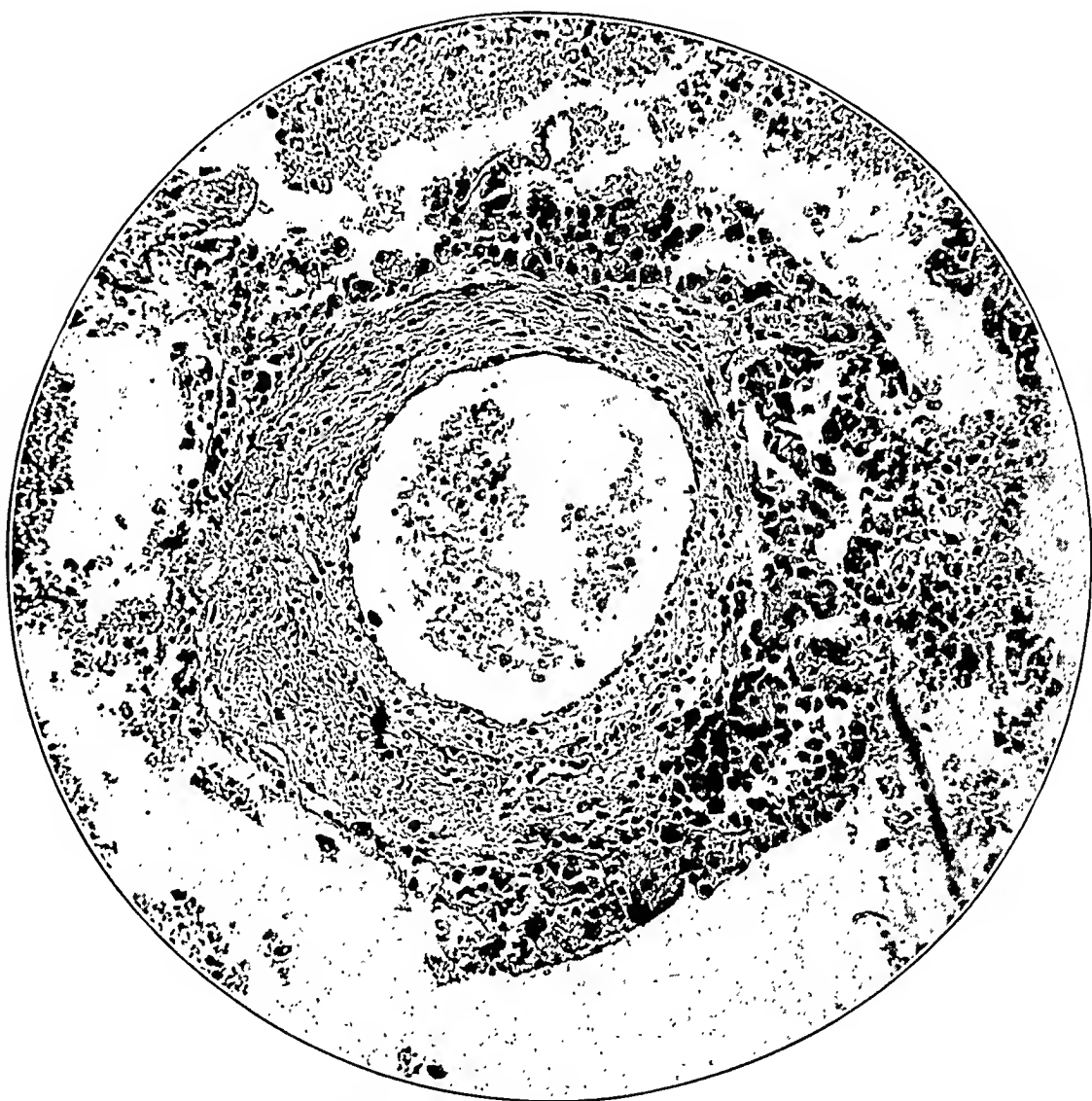


Fig. 2.—Blood vessels invaded and surrounded by tumor cells; hematoxylin and eosin stain; $\times 400$.

knee jerks were diminished, but the ankle jerks were present. There was a positive Babinski sign on the right. The patient was aphasic, chiefly on the emissive side.

Laboratory Data.—Examinations of the spinal fluid and the Wassermann reaction were negative. The blood picture presented a slight secondary anemia. The blood pressure was 100 systolic and 70 diastolic. The sputum was negative for tubercle bacilli. Roentgen examination of the left side of the chest showed a large mass in the superior mediastinum, the size of an apple. The edges were

Physical Examination.—Examination revealed a well developed and well nourished woman. There was limitation in motion of the right side of the chest, flatness anteriorly between the fourth and tenth ribs and posteriorly between the third and tenth ribs and absent vocal fremitus over the same area. Above these areas there was bronchial breathing. The other organs were normal, with the exception of a movable mass palpated in the right side of the abdomen. A hydropneumothorax in the right side of the chest with a tumor mass in the lower part of the right lung was considered.

Neurologic Examination.—There was exaggeration of the deep reflexes of all the extremities, with a twitching of the left hand. On March 26, 1928, a left hemiparesis, a papilledema of 2 diopters with retinal hemorrhages out of proportion to the amount of elevation and a bilateral Kernig sign with rigidity of the neck developed.

Laboratory Data.—The sputum was positive for tubercle bacilli on two or three occasions. A roentgenogram showed a dense shadow in the right side from the apex to the diaphragm, probably due to pleural thickening and pleural effusion. Examination of the skull gave negative results. The blood count showed red blood cells, 2,100,000; white blood cells, 9,800; hemoglobin, 65 per cent. The differential count was normal. The spinal fluid showed 40 cells and a slight amount of globulin. The cells were mononuclear. The Wassermann tests of the blood and spinal fluid were negative.

Diagnosis.—The clinical diagnosis was primary carcinoma of the lung superimposed on an old fibroid tuberculosis. The neurologic diagnosis was tuberculoma or tuberculous meningitis. The possibility of a metastatic neoplasm was considered. The anatomic diagnosis was papillary adenocarcinoma of the right lung with extension to the pleura and lymph nodes; metastases to the left lung, kidneys, suprarenals, retroperitoneal lymph nodes, liver and brain and uterine fibroids.

Autopsy Observations on the Brain.—The right hemisphere was larger than the left, with flattening of the gyri and sulci. When the brain was cut vertically in the anteroposterior direction, a marked swelling of the whole right hemisphere was found. At the tip of the right caudate nucleus, there was a small tumor mass measuring approximately 0.5 cm. in diameter. In the right upper parieto-occipital region (fig. 5), there was a large globular mass measuring 2 cm. in diameter extending to the outer surface and breaking through into the meninges. The center of the tumor was yellowish and necrotic. The rest of the central nervous system was free from metastases. Sections of the metastatic nodule to the brain at about the tip of the caudate nucleus consisted of alveolar masses lined by columnar type of cells. Between the glandular elements (fig. 6) there was a stroma of dense connective tissue, as well as a dense accumulation of apparent round cell infiltration in the necrotic areas. Some of the tumor cells had definite mitotic figures. The microscopic diagnosis was metastatic adenocarcinoma of the brain (bronchial in origin).

Comment.—This case showed a gradual onset of the pulmonary symptoms with a sputum positive for tubercle bacilli on several occasions. A diagnosis of neoplasm of the lung superimposed on an old fibroid tuberculosis was considered. The neurologic signs came on rather late and suddenly about one month prior to death, the diagnosis being tuberculoma, tuberculous meningitis or metastatic neoplasm. The

Comment.—The cerebral symptoms in this case came on suddenly with a fall, which undoubtedly was secondary (i. e., the fall) to the lesion in the brain. The age of the patient could easily have led one to make a diagnosis of cerebral hemorrhage. The careful examination of the chest and the roentgenogram of the chest prevented an error in the neurologic diagnosis.

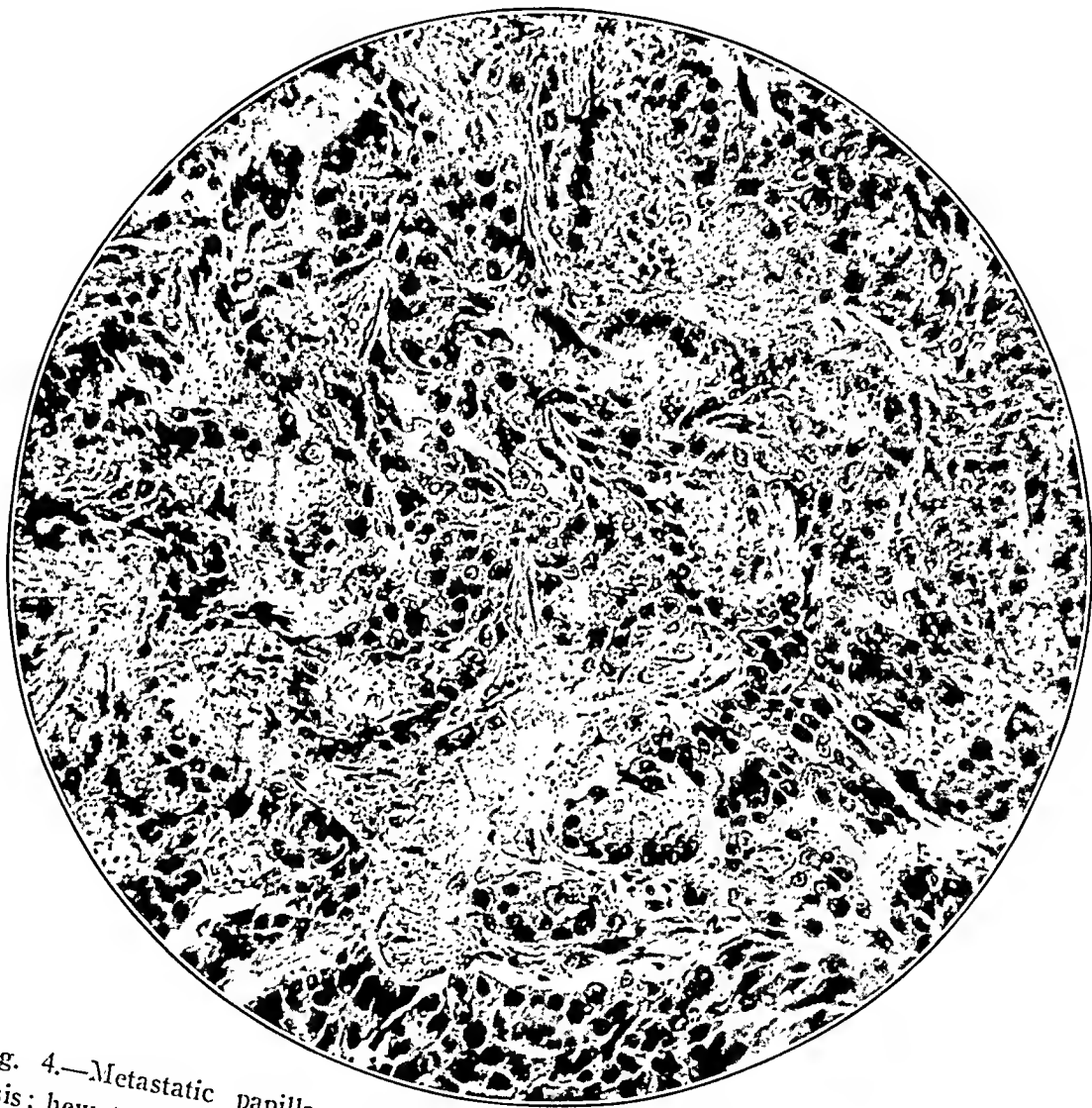


Fig. 4.—Metastatic papillary adenocarcinoma of the brain showing slight necrosis; hematoxylin and eosin stain; $\times 300$.

CASE 3.—History.—R. G., a woman, aged 34, a housewife, was admitted to the hospital on Jan. 11, 1928. In October, 1927, the patient caught cold. She had a temperature of from 100 to 101 F. for ten days, followed by cough, blood-streaked sputum and loss in weight. Dysphagia, pain in the throat and vomiting were present for eight weeks before admission. The past history was negative, except for a tracheotomy at the age of 5 following laryngeal diphtheria and a persistent cough and expectoration for six years.

posteriorly and anteriorly. Breath sounds were absent from the third interspace to the apex, and there were numerous moist râles. The left lung showed bronchial breathing at the base, with moist gurgling râles.

Neurologic Examination.—The patient was uncooperative and irritable and was disoriented as to time, place and person. Memory was poor for recent and remote events. Judgment was poor. She had some insight into her condition. There were no delusions, illusions or hallucinations. The positive neurologic obser-

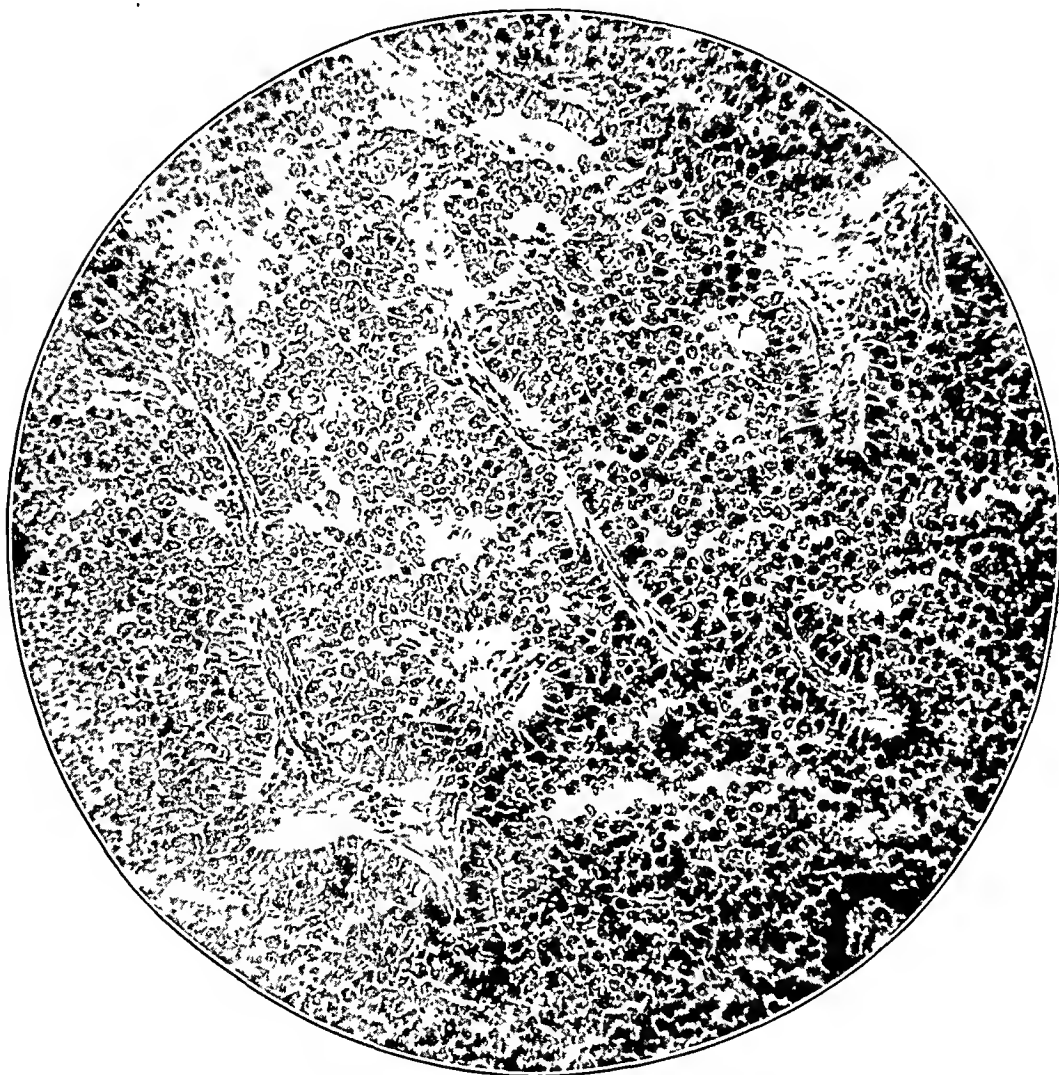


Fig. 6.—Metastatic adenocarcinoma to the brain; hematoxylin and eosin stain; $\times 300$.

ventions were: The pupils did not react to light or in accommodation; they were irregular and slightly unequal. The fundi showed bilateral choked disk. There was a general hyperreflexia, a bilateral Hoffmann sign, exhaustible ankle clonus and absent abdominal reflexes on the right, coarse tremor of both hands and tongue, difficulty in recognizing objects with the left hand and a suggestion of right finger-to-nose-ataxia.

bilateral Kernig sign, the rigidity of the neck and the sputum positive for tuberculosis led to a consideration of tuberculous meningitis. The metastases to the central nervous system were multiple. The histologic picture was that of an adenocarcinoma of the lung originating from the cells of the bronchus.

CASE 4.—*History*.—E. T., a woman, aged 40, an actress, was admitted to the hospital on Sept. 11, 1928, with a complaint of general weakness, irritability and incontinence of the sphincters. The patient, who had always been quarrelsome, became irritable in August, 1927. In a few months she began to cough, lost weight and became incontinent. In June, 1928, she became violent, and was sent to a state



Fig. 5.—Metastatic nodule of the right parieto-occipital region.

institution, where a diagnosis of dementia paralytica was made. Here she received five injections of arsphenamine. At this institution numerous râles were heard over both lower lobes posteriorly. The condition became worse, and later considerable consolidation of the left lower lobe of the left lung was noticed, with bronchial breathing and a moderate amount of fluid in the right side of the chest.

One brother had died of dementia paralytica, and one brother was being treated at the time for syphilis. She had been married for seven years and was separated from her husband. There had been no pregnancies or miscarriages.

Physical Examination.—Examination showed a fairly well developed but poorly nourished woman. The right cervical glands were palpable in the supraclavicular region. A gland the size of a walnut, firm, somewhat irregular and adherent to its bed was palpated in the anterior triangle of the neck. The lungs showed diminished resonance over the right apex and flatness in the right axilla

Comment.—The cerebral symptoms predominated in this case. The Argyll Robertson pupils, the history of a positive Wassermann reaction of the blood and the mental condition pointed to dementia paralytica, but the negative Wassermann test of the spinal fluid militated strongly against such a diagnosis. The presence of choked disk is almost unknown in dementia paralytica. This observation, with the suspicion

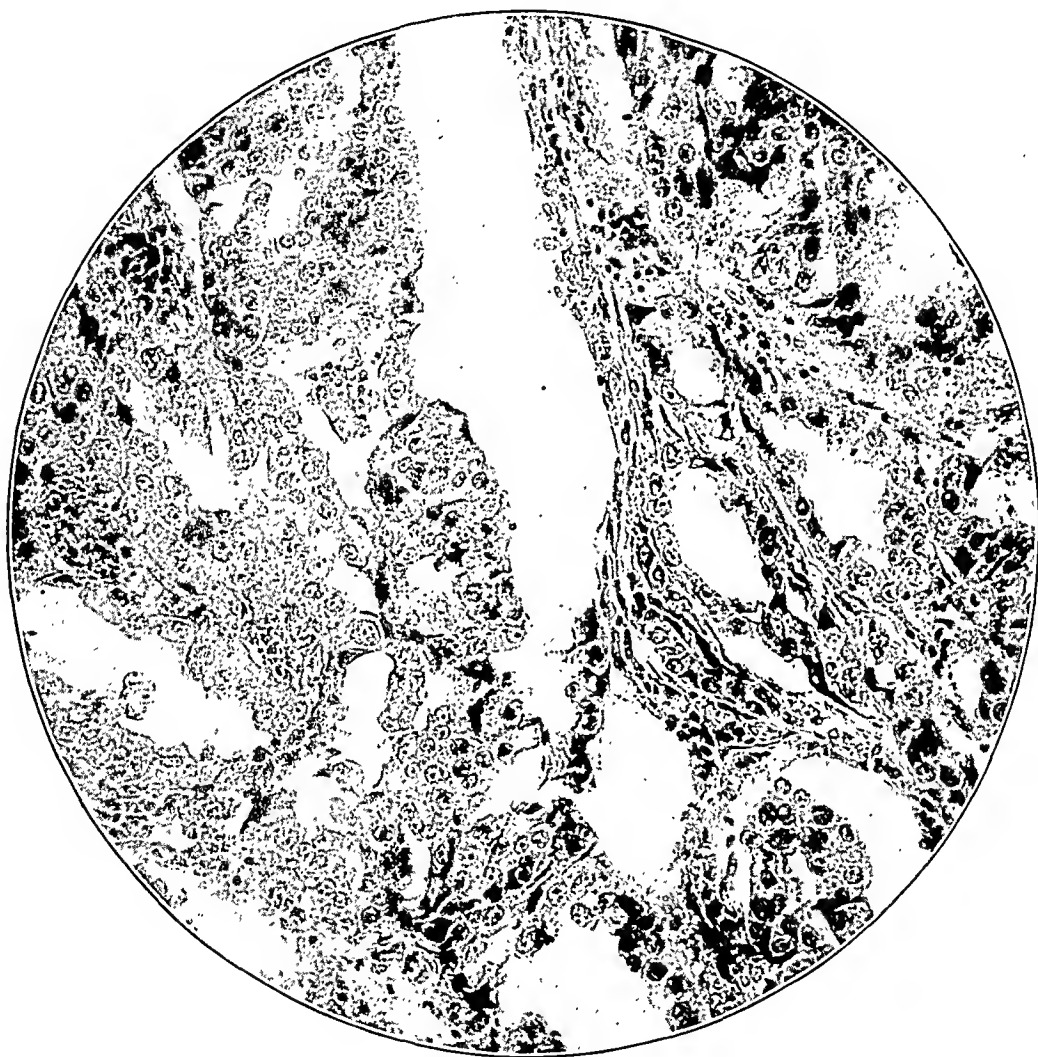


Fig. 8.—Metastatic papillary adenocarcinoma of the cerebellum; hematoxylin and eosin stain; $\times 300$.

of a left-sided impairment of stereognosis, led to the consideration of a cerebral neoplasm located in the parietal region. The only cerebellar sign was a suggestion of the finger-to-nose ataxia. Tumors of the posterior fossa have been described which give a mental picture similar to the one seen in tumors or neoplasm of the frontal lobe. The conjoint histopathologic observations of dementia paralytica and a cerebellar tumor easily explain the difficulty in the diagnosis. The obser-

were heard over the anterior and infraclavicular regions. The left lung showed no abnormalities. There was moderate clubbing of the fingers. The heart and abdomen were normal.

Neurologic Examination.—The right pupil was larger than the left; both reacted to light and in accommodation. All deep reflexes were hyperactive but equal. Other neurologic observations were negative.

Course.—The patient received deep roentgen treatments. He did well until May 11, 1929, when he fell and lacerated his scalp while attempting to get out of bed. Thereafter he began to complain of headaches and dizziness. There were no

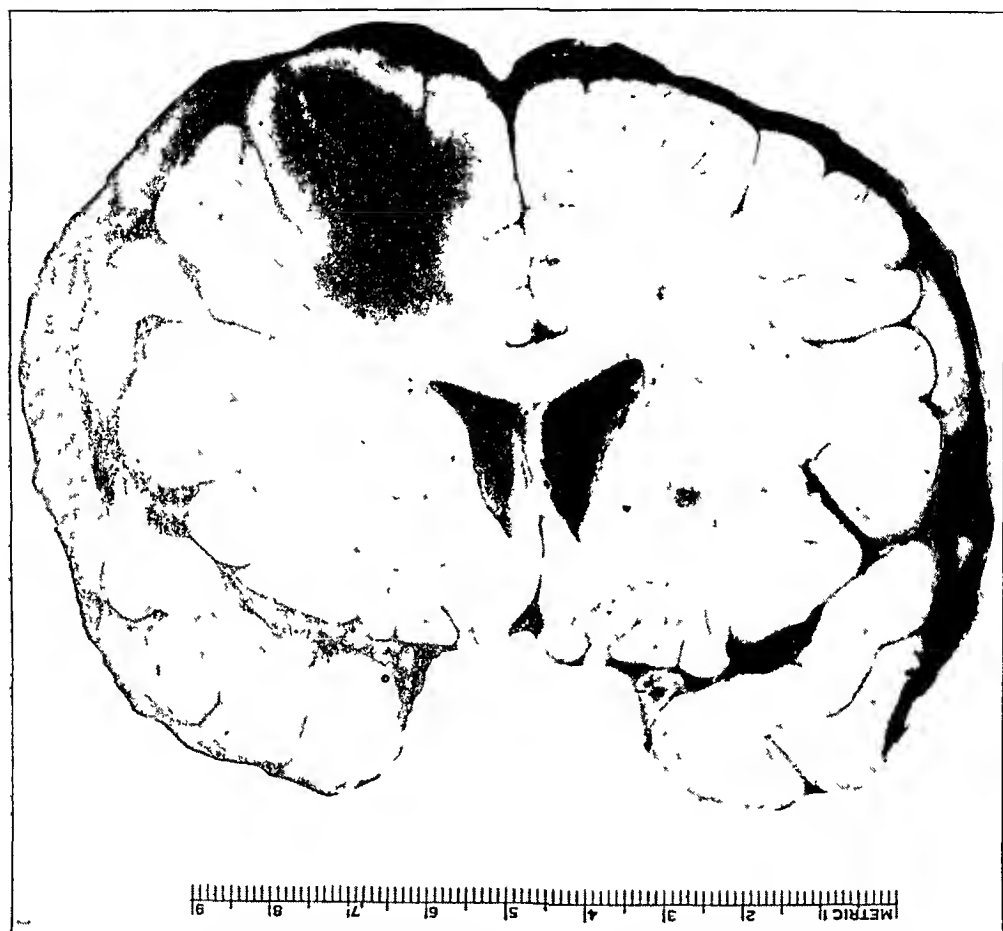


Fig. 9.—Hemorrhagic encapsulated mass in the prerolandic area with two small nodules located in the left corona radiata and caudate nucleus.

signs of fracture of the skull. A neurologic examination at this time showed nothing of note. The day before death (May 15, 1929) a temperature of 105 F. suddenly developed with signs of bronchopneumonia in the right lung.

Laboratory Data.—A roentgenogram of the chest showed numerous small calcified infiltrations in the upper lobe of the right lung and in the lower lobe partial consolidation which was suggestive of a neoplasm. Other laboratory examinations gave negative results.

Diagnosis.—The clinical diagnosis was primary carcinoma of the right lung. The anatomic diagnosis was carcinoma of the lung with metastases to the

vations on the chest were not interpreted, although a co-existent bronchopneumonia (which was probably terminal) superimposed on the new growth was found. There was evidence of involvement of the cervical lymph glands with a metastasis to the cerebellum.

CASE 5.—History.—S. L. a woman, aged 58, was admitted to the hospital on April 5, 1929. One year before admission the patient was troubled by a chronic cough accompanied by headache and tinnitus. In March, 1928, she had choking spells lasting from three to five minutes, during which period she became dyspneic. She later expectorated blood-streaked sputum. A diagnosis of pulmonary tuberculosis was made.

Physical Examination.—Examination showed a white woman, acutely ill, cyanotic, dyspneic and apprehensive. The pupils were unequal, the right being greater than the left, and regular and reacting promptly to light and in accommodation. Examination of the lungs was rather unsatisfactory on account of the patient's critical condition. The right lung showed flatness of the apex with hyperresonance below the clavicle. The left lung showed impaired resonance. Numerous moist, high-pitched râles were heard over the entire chest. Diffuse precordial pulsations were noticed.

Diagnosis.—The diagnosis was chronic fibroid phthisis, generalized arteriosclerosis, cardiac hypertrophy and dilatation and hypertension. The blood pressure was 194 systolic and 90 diastolic.

The patient died five and one half hours after admission.

The anatomic diagnosis was carcinoma of the bronchus with metastases to the lungs, pericardium, heart, tracheobronchial lymph glands, thyroid, liver, spleen, suprarenals, pancreas, ribs, skull, dura and pituitary; hydropericardium and multiple hemangiomas of the liver.

Autopsy Observations on the Brain.—The pia-arachnoid had a glistening appearance. The vessels were prominent, especially over the right Rolandic and Sylvian fissures. In the right prerolandic region there was a hemorrhagic encapsulated mass (fig. 9) with slight narrowing of the ventricle on that side. Additional nodules were found in the region of the diencephalon, globus pallidus, left caudate nucleus and in the pons. A few masses were found in both lobes of the cerebellum (fig. 10).

The histologic picture of the metastases to the brain showed a similar appearance to the original tumor mass. The microscopic diagnosis was metastatic papillary adenocarcinoma.

Comment.—This patient was in the hospital only five and one-half hours. A diagnosis of pulmonary tuberculosis was made. The interesting feature of this case was the metastasis to the heart muscle, a structure rarely involved by new growths. The involvement of the central nervous system was in the form of multiple metastases with a hemorrhage in the prerolandic area.

CASE 6.—History.—I. S., a man, aged 50, a merchant, was admitted to the hospital on Sept. 29, 1928, with the complaint of cough, hemoptysis and weakness which he had noticed for one year.

Physical Examination.—The right lung showed dullness anteriorly from the fourth interspace down and posteriorly from the seventh interspace to the base and axillary region. The breath sounds over these areas were diminished. Râles

Physical Examination.—The patient was markedly emaciated. The trachea was displaced to the right. There was drooping of the right shoulder. The right supraclavicular and infraclavicular fossae were deeper than the left. There was lagging of the left side of the chest, flatness of both apexes and cavernous breathing. All other organs were normal.

Neurologic Examination—There was complete immobility of the neck. The left pupil was irregular, and both pupils reacted sluggishly to light. There was a left Horner's syndrome with complete paralysis of the left lower extremities and

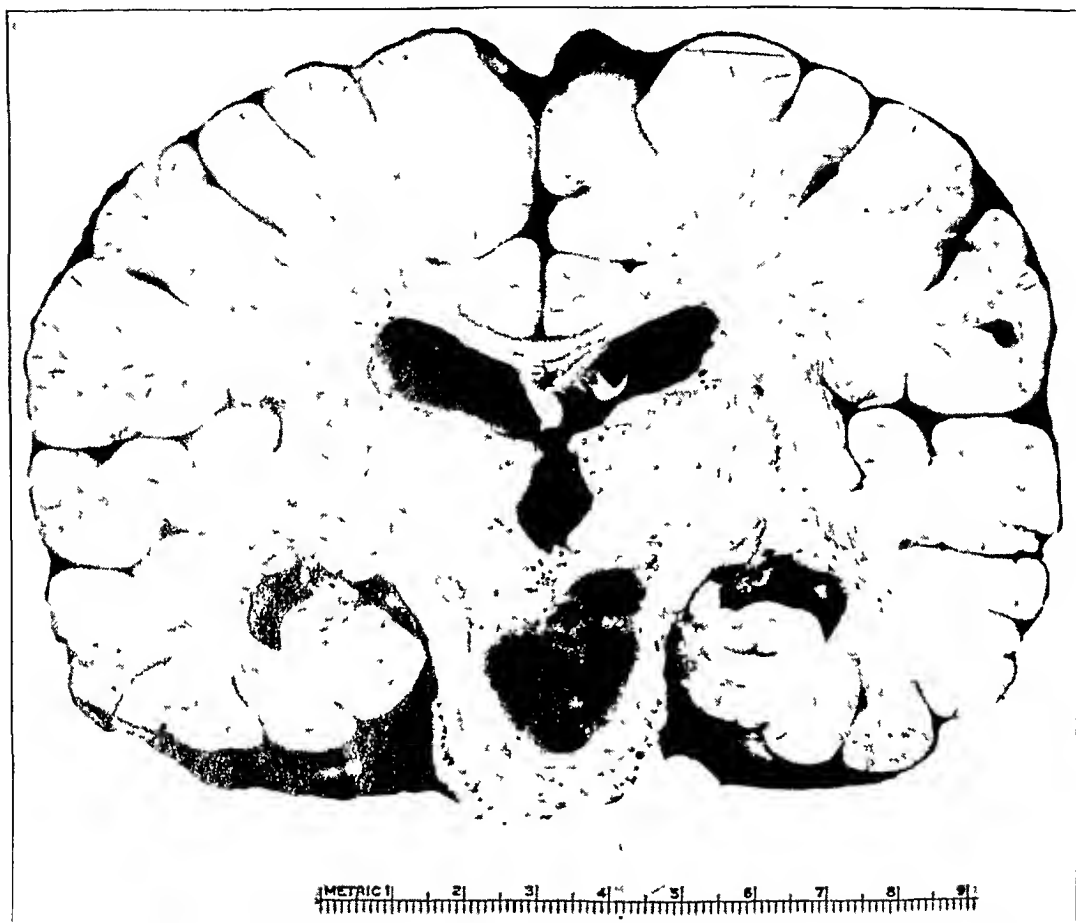


Fig 11—Metastatic tumor of the pons involving the pes pedunculi and substantia nigra.

paresis of the right lower extremities. All the deep reflexes were markedly diminished, the left more than the right. There was wasting of the thenar, hypothenar and interosseal muscles, more marked on the left. Sensation showed a belt of hyperalgesia at the third dorsal vertebra, below which level all forms of sensibility were either diminished or lost. The paralysis was flaccid.

Course.—Later a bilateral foot drop, flexion of the right lower extremity and a marked cystitis developed, and the patient died on July 21, 1929.

Laboratory Data—A roentgenogram of the thoracic spine disclosed a moderate degree of spondylitis, but no definite evidence of Pott's disease. The upper lobe of the left lung revealed a shadow extending from the apex to the fifth rib poste-

Sections below the level of the compression did not show any signs of descending demyelination. At the fifth and sixth dorsal vertebrae there was marked widening of the anterior spinal fissure with some destruction of the gray matter.

The tumor consisted of numerous fibroblasts which in places had a definite whorl formation. Between the fibroblasts numerous polyhedral-shaped cells with deeply stained, irregular nuclei were found. In places, these cells had a definite acinar arrangement; in others, they were densely grouped together. The dura was markedly thickened and invaded by the tumor cells. A few spicules of bone were found within the tumor tissue, probably from the breaking down of the vertebrae. The general appearance of the tumor, with the exception of the thickened dura, resembled the primary neoplasm in the lung which was bronchial in origin.



Fig 13—Extramedullary compression of the spinal cord by tumor mass causing distortion of the cord without marked degeneration of the white matter; Weil stain, $\times 10$.

Comment.—The condition in this case was considered as chronic pulmonary tuberculosis, although a neoplasm was thought of. This is the only case posted which disclosed a metastatic nodule to the cord causing its compression. Metastases to the vertebrae or cord are not so common as those found elsewhere in the central nervous system. The cord in this case did not show evidences of softening, as in some cases of compression in which the circulation of the cord is frequently interfered with.

Group 2—Cases of Primary Carcinoma of the Lungs Showing, Clinically Involvement of the Nervous System by Metastases in the Brains and Spinal Cords Which Were not Secured at Autopsy (Table 2)

riorly. The trachea showed displacement to the right. No definite statement could be made in regard to the state of the first, second and third dorsal vertebrae. The spinal fluid showed xanthochromia, 4 plus albumin and globulin and 4 lymphocytes, with evidence of partial block. The urine became loaded with pus cells before death.

Diagnosis.—The condition was diagnosed clinically as chronic bilateral fibroid tuberculosis, carcinoma of the left lung with metastases, compression myelitis of the spinal cord and chronic cystitis and pyelitis. The anatomic diagnosis was primary carcinoma of the lung with metastases to the vertebrae and liver.

Autopsy Observations on the Spinal Cord.—A small portion of the cord, to which a mass was attached, was removed from the upper dorsal region. On sectioning, the cord was seen to be distorted.

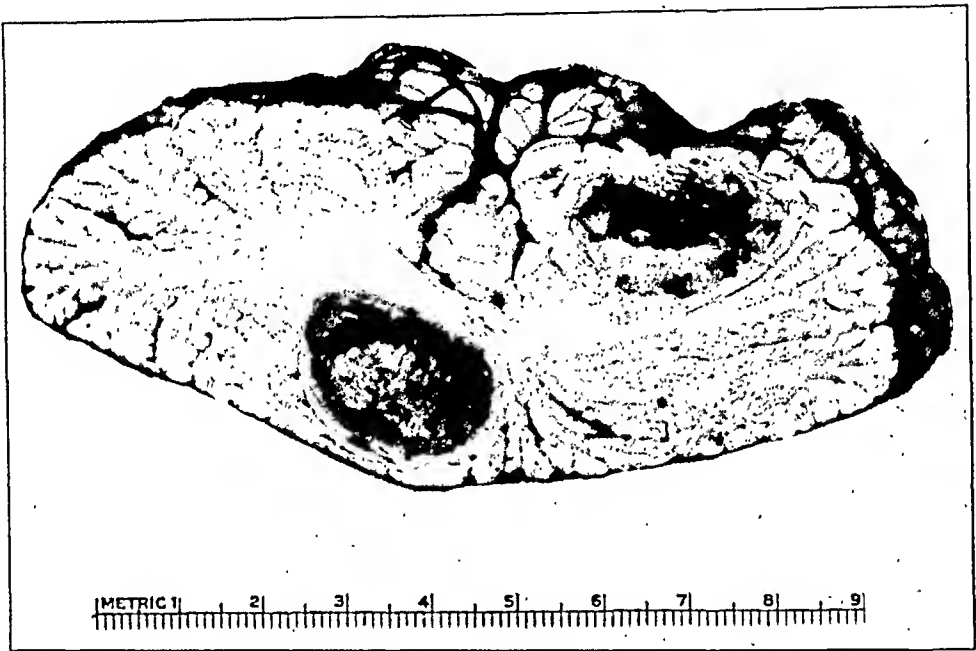


Fig. 12.—Metastatic tumor nodules to both lobes of the cerebellum.

Frozen and celloidin sections of the spinal cord were stained by the modified Loyez, hematoxylin and eosin, Mallory phosphotungstic, van Gieson, sudan IV, Cajal and Bielschowsky methods. The sections at the second dorsal vertebra with the modified Loyez method showed the outline of the cord to be markedly distorted with a tumor mass situated extradurally along the lateral surface of the cord (fig. 13). The vertical diameter was greater than the lateral diameter, the reverse of what is usually seen in the normal cord at this level. Under higher power magnification, there was no evidence of marked demyelination of the white fibers. With the cellular stains the anterior horn cells had undergone various changes, from disappearance of the Nissl substance to complete destruction. There were no evidences of compound granular corpuscles as seen in areas of softenings. With the glia stains, the glial elements did not show any changes. The blood vessels in the pia-arachnoid and within the cord were normal and did not show any signs of occlusion by the extradural mass.

With the Bielschowsky stain, the axis cylinders were fairly well preserved. Occasional axis cylinders showing swelling and corkscrew appearance were seen.

Laboratory Data.—Roentgen examination showed a dense homogeneous shadow from the apex to the diaphragm on the right side. The dorsal spine disclosed a partial collapse of the tenth dorsal vertebra. Examination of the hips showed a marked destruction of the acetabulum, especially at the upper half, with bone production. Examination of the sputum revealed tumor cells. The surgical specimen following paracentesis consisted of a few fragments of tissue made up of regular columns of foamy cells and small round nuclei.

Diagnosis.—The diagnosis was carcinoma of the lung with metastases to the spine.

Comment.—The tumor cells found in the sputum and pleural fluid, the roentgen observations on the chest and the partial collapse of the tenth vertebra with a definite picture of a transverse lesion of the spinal cord, pointed toward metastasis to the vertebral column. Nystagmus, as already observed by Elsberg and others, is not an uncommon observation in cases of lesion of the spinal cord, most likely due to involvement of the posterior longitudinal bundle.

CASE 3.—History.—S. C., a man, aged 47, a merchant, was admitted to the hospital on Sept. 4, 1926. In July, 1925, he had a dull pain over the right shoulder joint, which incapacitated him for work. A diagnosis of tuberculosis was made, and he was sent to Saranac Lake. In July, 1926, his speech became impaired; he stammered and at the same time dizzy spells and headaches developed. A diagnosis of carcinoma of the lung was made following a biopsy in September, 1926.

Physical Examination.—Examination revealed an unstable patient with a masklike expression of the face. The left half of the chest was slightly larger than the right. There was an impaired percussion note bordering to flatness over the left side of the chest from the fifth rib down. The breath sounds were diminished over these areas. The heart was normal.

Neurologic Examination.—The pupils were normal and reacted to all stimuli. The right forearm, arm and hand showed atrophy of the muscles. The power of the right hand was poorer than that of the left, and the entire shoulder joint and back were one solid mass. Movements of the shoulder joint were limited. There was some hyperesthesia over the right upper extremity. The patient was disoriented for time, was apathetic, restless and emotionally unstable and had definite memory defects. There were no illusions, delusions or hallucinations. He was discharged from the hospital on Oct. 3, 1926.

Laboratory Data.—A roentgenogram of the chest showed a pleural effusion on the left side extending from the diaphragm up to the fourth rib in the axillary line. Above this there was a complete pneumothorax, the upper lobe being collapsed down to a small mass. The heart and mediastinum were pushed to the right. There was a dense mass around the right shoulder joint, with a destructive process involving the entire scapula and the outer and middle thirds of the clavicle suggesting a neoplasm. Examination of the skull failed to reveal any metastases. Other laboratory examinations gave negative results. Fluid tapped on Sept. 20, 1926, was hemorrhagic and contained tumor cells suggesting a primary neoplasm of the lungs.

Diagnosis.—The diagnosis was carcinoma of the lung, with secondary involvement of the right shoulder, brain and liver.

CASE 1.—History.—M. D., a man, aged 48, a milkman, was admitted to the hospital on Dec. 19, 1923, complaining of pain in the right side of the chest, the right calf and the back of the neck for the past three weeks. In October, 1923, the patient caught cold, following which a severe cough and pain developed on the right side. He noticed difficulty in starting to urinate and later had to be catheterized. At this time, he noticed pain in the right calf and began to lose weight.

Physical Examination.—Examination showed an emaciated man with a generalized wasting over the entire body. There was lagging of the chest on the right side, with flatness on percussion posteriorly. Occasional moist, crackling râles were heard over the same area. The breath sounds were barely perceptible posteriorly. The blood pressure was 110 systolic and 80 diastolic.

Neurologic Examination.—The pupils were small and equal and reacted well to all stimuli. The upper reflexes were moderately increased, with a suggestive Babinski sign on the left. The patient was unable to use the left leg and was incontinent. He died Jan. 23, 1924.

Laboratory Data.—On roentgen examination a large mass was seen extending from the hilus at the level of the sixth to the tenth ribs infiltrating the pulmonary tissue. Other laboratory examinations gave negative results.

Diagnosis.—The diagnosis was carcinoma of the lower lobe of the right lung.

Comment.—The neurologic signs were rather indefinite, and cerebral or spinal cord localization was difficult. A possibility of both spinal cord and cerebellar involvement was most likely. Autopsy was not performed.

CASE 2.—History.—N. B., a man, aged 46, an employment agent, was admitted to the hospital on Feb. 6, 1926, with pain in the right side of the chest of fourteen months' duration. In November, 1924, while at his clerical work, he suddenly dropped his pen and experienced a sensation of numbness over the right hand. This extended down to the elbow, and three weeks later he observed burning pains in the right shoulder and right side of the chest posteriorly. A diagnosis of syphilis was made, and he received antisyphilitic treatment. About March, 1925, he noticed a bulging of the left eye. At this time he received roentgen treatments to the chest. The shooting pains extended to the left leg, and a few weeks later difficult and painful urination developed.

Physical Examination.—The patient was poorly nourished and markedly emaciated. He was confined to bed, with the lower extremities flexed on the abdomen. The left eyeball was more prominent than the right. The left side of the chest was bulging. The expiratory movements on the right side were limited from the apex to the base. There was absent vocal fremitus over the entire right side, with dullness to flatness from the third rib down. There were diminished to almost absent breath sounds on the right side from the third rib to the base of the lung. The blood pressure was 110 systolic and 74 diastolic.

Neurologic Examination.—The left pupil was greater than the right; both were irregular and both reacted sluggishly to all stimuli. There was nystagmus in the right-left lateral gaze. All the deep reflexes were increased. The knees were flexed on the abdomen. There was marked tenderness of the left hip. There was a definite zone of hyperesthesia, hyperalgesia and hyperthermesthesia on the right side, corresponding to the fourth and fifth dorsal vertebrae.

by loss of weight and weakness. He received four deep roentgen treatments over the chest, following which the cough became more productive and bloody. On January 23, the lower extremities became completely paralyzed, with loss of sensation to the nipple line. The paralysis was preceded for a few hours by a gradual weakness, clonic movements of both lower extremities and loss of control of the bladder and rectum.

Physical Examination.—The patient was a well developed man. The glands of the neck were somewhat enlarged in the supraclavicular region. There was irregular expansion on both sides of the chest with dulness at the left base and impaired note throughout the entire right side. The breath sounds were distant, with many moist, coarse and fine râles over the right side of the chest. The heart was normal.

Neurologic Examination.—The pupils were irregular; the right was larger than the left, and both reacted to all stimuli. There was a flaccid paralysis of both lower extremities with absent reflexes. All forms of sensation were lost from the eighth dorsal vertebra down. The biceps and triceps were elicited and were equal on both sides. There was retention of urine with a relaxed rectal sphincter.

Diagnosis.—The clinical diagnosis was carcinoma of the lung with metastases to the dorsal spine.

Laboratory Data.—Slight secondary anemia was present. The urine was normal. The patient died on Feb. 5, 1928.

The anatomic diagnosis was carcinoma of the upper lobe of the right lung, with invasion of the ribs and vertebral column; metastases to the bronchial and retroperitoneal lymph nodes; subacute urethritis and pyelitis and hypostatic pneumonia in the lower lobes of both lungs. The brain and cord were not removed. The microscopic diagnosis was primary carcinoma of the lung originating from the bronchi.

Comment.—The sudden onset, the definite primary carcinoma of the lung and the level lesion of transverse myelitis at the eighth dorsal vertebra pointed to metastases to the vertebra. The cerebral symptoms were completely absent.

The analysis of the cases that came to autopsy (sixty-one in all) showed fifty-seven of the tumors to be bronchial in origin; two were squamous cell carcinomas, one originated from the alveoli of the lungs and one belonged to the primary endothelial type of tumor. The histopathology of these types of tumors is fully covered by Ewing,⁷ Moise⁸ and others, and for a detailed account the reader is referred to these authors.

In group 1 the ages ranged from 34 to 70; the average duration of the tumor was about from one to one and one-half years, with the exception of case 2 in which the patient lived nine years and case 3 in which the patient lived six years. The pulmonary signs came on sud-

7. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922, pp. 809-815.

8. Moise, T. S.: *Primary Carcinoma of the Lungs*, *Arch. Int. Med.* **28**:733 (Nov.) 1921.

Comment.—The character of the tumor cells from the fluid, the biopsy in 1926, and the mental and neurologic signs pointed toward involvement of the central nervous system, as well as the right brachial plexus. As in many other cases, during the early course of the disease, a diagnosis of pulmonary tuberculosis was considered. This patient died at home, and an autopsy was not secured.

CASE 4.—A. K., a woman, aged 56, a housewife, was admitted to the hospital on Oct. 1, 1927, complaining of cough, loss of voice and gradually increasing weakness of the left half of the body. The onset took place one year before admission to the hospital, with chills and fever; the condition was diagnosed bronchitis. In February, 1927, the patient began to complain of flushing of the face, dry tongue and paresthesias of the face and arms, with a gradual paralysis of the left side of the body. She was taken to a hospital, where a diagnosis of chronic encephalitis was considered. There paroxysmal attacks of coughing developed, and toward the end she became hoarse and aphonic. She had two convulsions, preceded by attacks of aphonia without loss of consciousness.

Physical Examination.—Examination showed a well nourished, somewhat distressed woman with slight cyanosis of the lips and paralysis of the left side of the mouth. On percussion, flatness was found over the middle and lower portions of the left side of the chest and over the right angle of the scapula. Moist coarse râles were audible posteriorly over the entire right side of the chest. The breath sounds over the left side were diminished. The heart was normal.

Neurologic Examination.—Exophthalmos was noted. The fundi revealed changes incidental to a high myopia. Speech was reduced to a whisper. There was a definite left hemiplegia with active biceps and ankle jerks on both sides. There was a Babinski sign on the right. On Oct. 4, 1927, the patient had a Jacksonian attack. She died on Oct. 25, 1927.

Laboratory Data.—A roentgenogram of the chest showed a pleural effusion on the right side extending to the sixth rib in the axillary line, possibly due to neoplasm. The blood count showed: hemoglobin, 50 per cent; red blood cells, 2,200,000; white blood cells, 14,800. The differential count was normal. A Wassermann test of the blood and spinal fluid was negative.

Diagnosis.—The condition was diagnosed neoplasm of the lung, with cerebral metastasis. The anatomic diagnosis was squamous cell carcinoma of the right lung, right bronchus, with extension and metastases to the bronchial lymph nodes and compression of the esophagus; chronic pyelitis and cystitis.

The brain and cord were not removed.

Comment.—Early during the disease, a diagnosis of chronic encephalitis was considered. Unlike most cases, the onset of the disease was gradual. The presence of the tumor in the lungs most likely was the explanation of the neurologic observations. The histogenesis of the tumor showed it to belong to the squamous cell variety.

CASE 5.—History.—S. S., a man, aged 53, a cap maker, was admitted to the hospital on Jan. 12, 1928, with paralysis of the lower extremities and loss of sensation below the nipple line, pain in the right side of the chest and bloody expectoration. The onset came on suddenly five months before admission with sharp pain in the right side of the chest, which was worse on coughing, followed

of the spinal cord, symptoms of which were undoubtedly due to secondary deposits in the vertebral column causing compression of the cord. Case 2 disclosed a partial collapse of the tenth dorsal vertebra, which was verified at autopsy. Only two of the cases in this group in which the condition was diagnosed as carcinoma of the lung came to autopsy (cases 4 and 5), and the brains and spinal cords were not removed.

SUMMARY

A group of 12 cases selected from 109 in which the condition was diagnosed as primary carcinoma of the lung were studied from the point of view of metastases of the central nervous system.

Three cases showed symptoms of the spinal cord due to compression following invasion and destruction of the vertebra by the metastases. Of 109 cases of primary carcinoma of the lungs investigated, 11 per cent showed involvement of the central nervous system. One of the cases came to autopsy and revealed compression and distortion of the cord without circulatory interference. The spinal cord is rarely the seat of metastasis from primary carcinoma of the lung.

The onset in most of the cases showing neurologic signs came on suddenly. The neurologic signs may be present without any evidence of pulmonary changes. For both diagnostic and therapeutic reasons, thorough examination and roentgenograms of the chest are advisable in every case in which tumor of the brain is suspected.

Metastases to the central nervous system may be single or multiple. When multiple metastases are found, the theory of tumor cells being carried by the blood stream to the brain is favored. When a single metastasis is found, a direct extension by a backward flow of the lymph to the brain due to involvement of the cervical lymph nodes is favored.

The most frequent histologic types of primary carcinoma of the lung with or without metastases to the central nervous system were those derived from the bronchi.

1929. In the latter years, the diagnosis was measurably fortified by studies of blood volume. No cases have been included in which the likelihood of polycythemia vera being present had been graded, at the time of diagnosis, as less than 75 per cent. The features of each case have been reviewed in detail and the diagnoses verified. All cases in which obvious thrombosis of peripheral veins was present have been excluded. Of this number, twenty-seven cases (27 per cent), presented a major complaint referable to the extremities, which suggested disease of the arteries of the extremities. In view of lack of special interest in the problem, and incomplete studies in most of the early cases, it is almost certain that the figures given represent an underestimate of the incidence of the conditions considered. The observations reported, however, are the result of a more intensive interest developed in recent years, and are in themselves, to our minds, satisfactory. These cases were classified in three groups: a group of arteriosclerotic patients, a

TABLE 1.—*Polycythemia Vera*

Total cases	100
Cases in which major complaint is referable to extremities (not including those of venous thrombosis)	27
1. Arteriosclerotic disease	20
a. Claudication without demonstrable occlusion.....	6
b. Arterial occlusion with gross gangrene.....	1
c. Aeroparesthesia (burning type).....	13
2. Thrombo-angiitis obliterans	1
3. Vasomotor disturbances	6
a. Dilator type (some features of erythromelalgia).....	3
b. Spastic type (features suggesting Raynaud's disease).....	3

group with thrombo-angiitis obliterans, and a group in which vasomotor disturbances were prominent (table 1).

ARTERIOSCLEROTIC DISEASE

In these cases sclerosis and calcification of the arteries of the extremities were present in a greater degree than was felt compatible with the age of the patient. The symptoms were attributable to arterial insufficiency.

Claudication.—In the six cases of arteriosclerosis of the extremities in which there was claudication, without occlusion of palpable arteries, claudication was a definite and disabling symptom. Distress on exercise was usually localized in the feet and calves of the legs; in two cases, claudication was bilateral. Exercise was restricted after periods of walking from two to six city blocks. Relief was obtained by standing still for short intervals, after which exercise could be resumed. In all the cases of this group, high grades of calcification were represented in the roentgenograms.

PERIPHERAL ARTERIAL DISEASE IN POLYCYTHEMIA VERA *

GEORGE E. BROWN, M.D.

AND

HERBERT Z. GIFFIN, M.D.

ROCHESTER, MINN.

The commonest complications of polycythemia vera are those of the vascular tree. The frequency of thrombosis is generally recognized, and it is demonstrable that venous thrombosis is present in the majority of cases of polycythemia vera when they are first seen. The high incidence of thrombosis seems to be adequately explained by the huge increase in the volume of circulating blood of high viscosity. After the disease has persisted for a time, sluggish circulation, with chronic passive congestion, becomes exaggerated. The rate of circulation, as tested by the histamine method, when measured from leg to face or arm to face, is from five to ten times slower than that in the normal subject. There are changes in the blood, also, which favor thrombosis; high viscosity, hypercalcemia, and an increase in the number of platelets doubtless are important.

The arterial diseases associated with polycythemia vera have not been extensively studied. An impression has been gained from roentgenograms of the peripheral arteries, in cases of polycythemia vera, that abnormal grades of calcification exist, especially in patients of advanced age. The symptoms and the appearance of the retinal vessels have led to the suspicion that cerebral arteriosclerosis is common. Peacock, in a recent study, has shown that the arterial pressure is not increased to a significant degree in polycythemia vera, in spite of the huge increase in the volume of blood. The lack of accurate data on the subject led to this study of a group of cases of polycythemia vera in which certain features seemed to be secondary to arterial disease.

MATERIAL USED FOR THE PRESENT STUDY

One hundred cases in which the diagnosis of polycythemia vera had been made were reviewed with reference to symptoms which might be regarded as indicative of peripheral arterial disease. This series includes all of the cases seen at the Mayo Clinic from May 1, 1912, to Jan. 1,

* Submitted for publication, March 27, 1930.

* Read before the Association of American Physicians, Atlantic City, N. J., May 8, 1929.

* From the Division of Medicine, the Mayo Clinic.

Arterial Occlusion with Gangrene.—It might be expected that gangrene of arteriosclerotic origin would be relatively common in this disease; however, only one case of this type was encountered. In order to obtain more accurate information on this point, studies of blood volume have been made in cases of gangrene of arteriosclerotic origin. In several cases of gangrene, there was relative polycythemia, in which the number of erythrocytes for each cubic millimeter of blood and the concentration of hemoglobin, was increased, but the blood volume was not above normal limits. These cases of relative polycythemia were similar to the type described by Geisböck as polycythemia hypertonica. The patient with true polycythemia and arteriosclerotic gangrene was a senile man, aged 78. When he was first seen he had bilateral pedal gangrene, with an excessive degree of generalized cyanosis. Because of excessive pain he had taken many tablets presumably containing derivatives of coal tar. Spectroscopic examination of the blood disclosed the presence of sulphemoglobin. He had 171 cc. of blood for each kilogram of body weight. The spleen was moderately enlarged, and the number of erythrocytes and the percentage of hemoglobin were high. His condition was so critical that operative measures could not be carried out. He returned home, and died within a month.

Acroparesthesia.—Thirteen patients in this series gave as their major complaint a burning sensation of the feet. Cases were not included in which numbness and creeping paresthesia were prominent. The usual symptoms were burning distress with exercise, or at night alternation of coldness of the limbs with burning distress, and cramps of the muscles of the calf. Accurate segregation of the patients with acroparesthesia, and those with a vasodilator syndrome, was accomplished by thermometric and calorimetric studies during the stages of burning. Three groups could be distinguished: (1) patients with acroparesthesia, without variations in the surface temperature in the stages when there was burning; (2) patients with acroparesthesia and slight increases in surface temperature during the symptomatic period, insufficient, however, to be considered significant as a causative factor in the complaint, and (3) patients with a true vasodilator syndrome, with high surface temperature and other phenomena making possible the diagnosis of erythromelalgia. The third group is considered under the dilator type of vasomotor disturbance; the first and second groups are classified as true acroparesthesia. Neurologic changes were not demonstrable in this group with acroparesthesia. Calcification and coldness of the feet were common; claudication was absent. The explanation of the frequency of this syndrome in polycythemia vera is not clear, although many theories have been advanced.

THROMBO-ANGIITIS OBLITERANS

One patient with a proved case of thrombo-angiitis was observed. The patient, an American born gentile, aged 52, came to the clinic with gangrene of the first toe on the right foot. Because of his heightened facial color, the volume of the blood was determined, and was found to be 160 cc. for each kilogram of body weight. Improvement was not effected in the condition of the extremity by reduction of blood volume and the right leg was amputated. Figure 2 shows the appearance of the arteries. The pathologic picture was that of a mixed lesion. There was definite arteriosclerosis, as was shown by the calcification of the

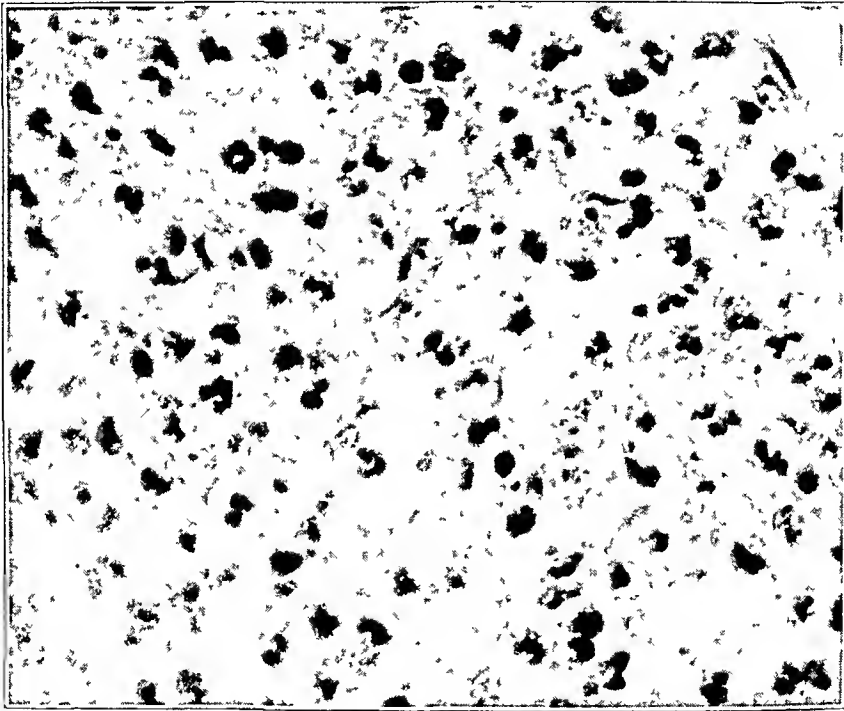


Fig. 3.—Appearance of cells in occluding thrombus. Lymphocytes and polymorphonuclear cells predominate.

media, but the occluding thrombus was of the inflammatory type (fig. 3). Magnification under high power disclosed the presence of many polymorphonuclear leukocytes and lymphocytes. In the outer coats of the arteries, also, there was definite inflammatory reaction. Weigert's stain (fig. 2) revealed great thickening of the intima in the nonthrombosed areas. There was marked proliferation of the elastic tissue layer.

VASOMOTOR DISTURBANCES

Dilator Type.—Three patients of the series presented symptoms suggesting erythromelalgia. There were excruciating degrees of burning, usually in certain areas on the plantar surfaces of the feet. The

Müller suggested a vasoneurotic basis, which is not borne out by our studies. Cassirer suggested disturbance of the sensory nerve endings, to which opinion we incline. Our conception of the disturbance postulates atrophy of the outer layer of the skin secondary to vascular changes in the smaller arteries of the skin, probably on an arteriosclerotic basis. Irritation of nerve endings results from stimuli not ordinarily perceived in normal skin. Vasomotor reflexes of a vasoconstrictor type would also be present in many instances.

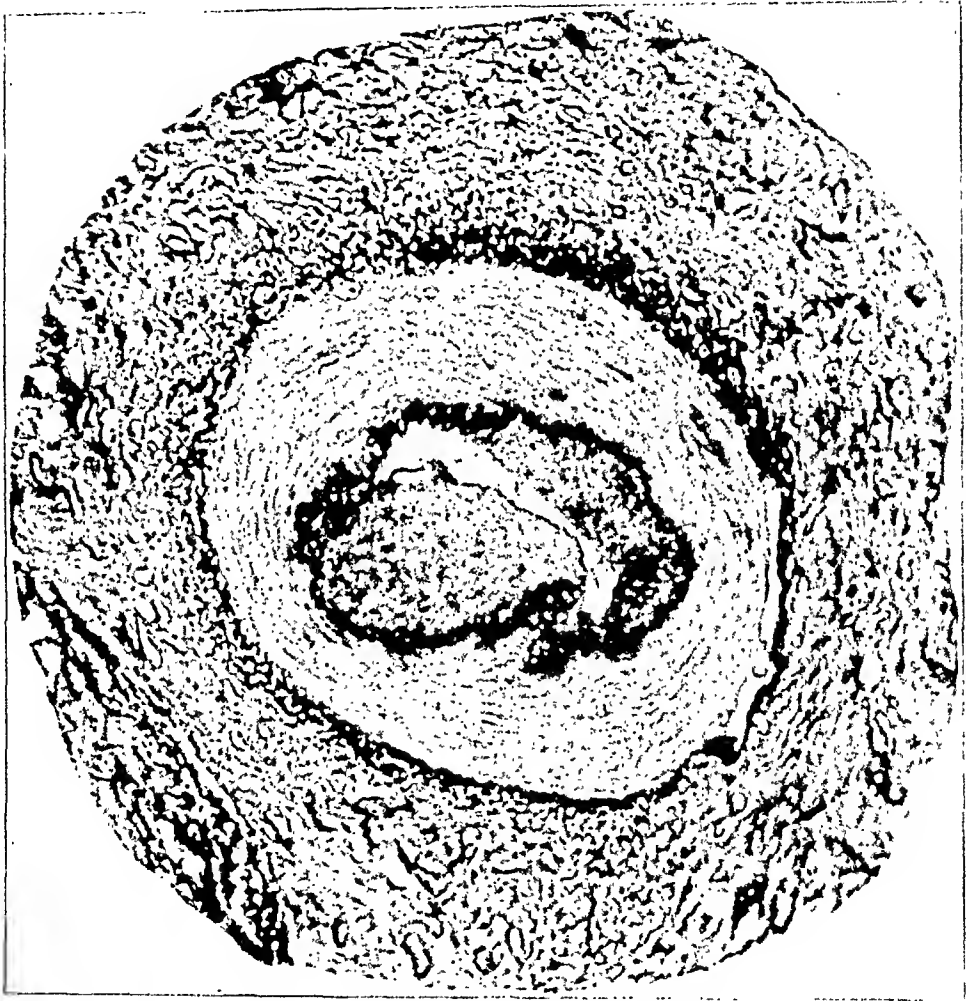


Fig. 2.—Appearance of artery in polycythemia vera and thrombo-angiitis obliterans. The partial occlusion of the arterial lumen is due to intimal proliferation. A thrombus is not shown in this area. Weigert's stain is used to show proliferation of the elastic tissue.

In this group of cases there is absence of relief following reduction of blood volume. Indeed, no form of treatment has been successful in relieving this burning paresthesia. Contrast baths and cinchophen have given only slight symptomatic relief. Apparently, increased viscosity and a slow rate of circulation are not direct factors in the production of acroparesthesia.

weight, relief of approximately 50 per cent was produced in the symptoms. Reports from this patient obtained during the ensuing year have indicated persistence of vasomotor disturbances; the intensity of the symptoms increases and decreases with some apparent relationship to the polycythemia, but at no time has complete relief been obtained. Figures 4 and 6 show the surface temperatures of the right foot and the left foot, and the effects of posture, exercise and weight-bearing on the surface temperatures. The marked difference between the feet is striking.

The second case of the series was that of a woman, aged 72, who was first seen in 1926 complaining of paroxysmal attacks of burning

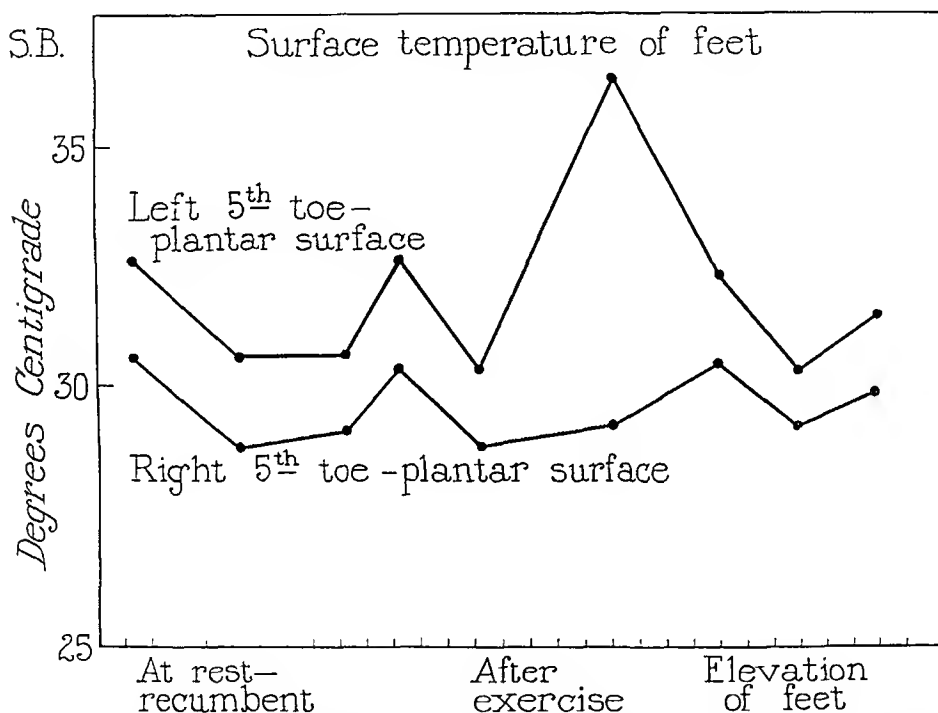


Fig. 4.—Increase in the surface temperature in a case of unilateral vasodilator disturbance, at rest, after exercise and with elevation of the feet.

feet, which were induced by exercise, and by covering the feet in bed. The symptoms suggested the syndrome seen in older subjects with arteriosclerosis. The elevated surface temperature during attacks, however, demonstrated that this was a true vasodilator disturbance. At this time, 1926, the concentration of hemoglobin and erythrocytes was normal, whereas the viscosity of the blood was somewhat high, 6.3. The patient was carefully observed at home for the next two years, at the end of which time she returned for detailed examination. It was then found that the vasomotor disturbances had entirely disappeared, and that definite evidence of polycythemia vera had developed. The volume of blood was 191 cc. for each kilogram of body weight, and mild hyper-

burning was intermittent and was aggravated by heat and exercise, and by a dependent position of the extremity. Moderate relief was obtained by elevation of the feet and by applications of cold. During the attacks, the feet or hands would become excessively red, the veins engorged, and the surface temperature of the painful area markedly elevated. The data in one of these cases are shown in table 2. The patient was a Jew who presented a picture of vasodilator neurosis involving his left foot. The fact that the disorder was unilateral separated it from the syndrome described by Mitchell which is always bilateral. When

TABLE 2.—*Thermometric Studies of a Case of Unilateral Erythromelalgia and Polycythemia Vera in a Man, Aged 25*

Date	Mouth	Room	Temperature, C.		Position	Comment
			Skin			
			Right Great Toe	Left Great Toe		
1/ 2/28	37	22	27.5	34.3	Patient at rest	Blood volume 203 cc. for each kilogram of body weight Burning pain in left foot
			31.0	31.8	Patient at rest	
			30.1	33.2	Feet up 45°	
			30.0	34.1	Feet up 90°	
			30.3	34.1	Feet down 45°	
			28.8	33.8	Feet down 90°	
			28.3	33.8	Blood pressure cuffs above the knees cutting off pulse of both feet	
			27.5	33.5	Patient at rest	
			29.0	34.3	Feet up 90°	
			30.7	34.1	Rapid walking exercise	
1/19/28	37	22	29.7	31.9	Patient at rest	No distress in left foot
			29.3	31.9	Patient at rest	
			27.5	28.7	Feet up 45°	
			31.1	31.9	Feet up 90°	
			29.7	31.5	Feet down 40°	
			28.2	30.0	Rapid walking exercise	
1/21/29	Blood volume 150 cc. for each kilogram of body weight. Relief 50 per cent in left foot

the patient was first examined, he had 203 cc. of blood for each kilogram of body weight. The surface temperature of the affected foot, during the attack, increased to 34.3 C. (93.5 F.), while that of the opposite foot was 27.5 C. (81.5 F.) (fig. 4). Calorimetric studies disclosed definite differences in the rate of elimination of heat as measured in small calories in the two feet (fig. 5). It was found that elevation of the foot diminished the temperature on the affected side appreciably, whereas on the normal foot only a slight change occurred. Likewise, cutting off the circulation on both sides for a period of fifteen minutes produced no lowering of the cutaneous temperature on the affected side, but a slight reduction of that of the skin of the normal foot. With the reduction of the blood volume to 150 cc. for each kilogram of body

tension was present (table 3). The temperature of the surface of the extremities at this time was normal, varying between 26 and 28 C. (78.8 and 82.4 F.), and peripheral symptoms were absent.

The third case was similar to the second case. The patient was aged, and complained of burning extremities in which the surface temperatures and calorimetric studies indicated vasodilator disturbances. The blood volume was 150 cc. for each kilogram of body weight. The clinical appearance was that of polycythemia vera; splenomegaly was present. Marked improvement was obtained in this case by reduction of the blood volume.

TABLE 3.—*Data in a Case of Erythromelalgia in a Woman, Aged 72*

Temperature, C.						
Date	Mouth	Room	Skin Temperature of Foot			Comment
			Right Dorsum	Left	Left Dorsum	
				Plantar Surface		
1/15/26	22	34.4	35.5	Paroxysmal attacks of hot burning feet induced by exercise and bed covers
9/22/26	37.1	23	34.7 35.0	34.7 35.2	
9/24/26	36.1	22.4	36.0 35.3	35.0 34.6	Blood data: hemoglobin, 16.5 Gm. for each 100 cc., 4,920,000 erythrocytes for each cubic millimeter; viscosity, 6.3
9/29/26	35.1 35.5	34.4 34.7	
9/ 4/28	Patient returned with complete relief from symptoms in feet; diagnosis: polycythemia vera (191 cc. of blood for each kilogram of body weight) and hyperthyroidism

Spastic Type.—Vasomotor disturbance of the spastic type was relatively rare. This seems rather surprising in view of the fact that vasospasm of the smaller arterioles involving single digits is not uncommon in cases of arteriosclerosis. In three cases, attacks of pallor occurred, which involved single digits, and were asymmetrical in distribution. This is the so-called "dead finger" syndrome, or the single phase color reaction observed in the secondary forms of vasomotor disturbances of the spastic type. Recovery of the arteriolar spasm was easily induced by immersion of the hands in warm water or by active massage. Trophic changes were not observed. Microscopic examination of the surface capillaries revealed the long, narrow, contracted loops seen in cases of arteriosclerosis. The dilated atonic capillary loops of Raynaud's disease were absent. Reduction of blood volume in these cases caused complete disappearance of the symptoms.

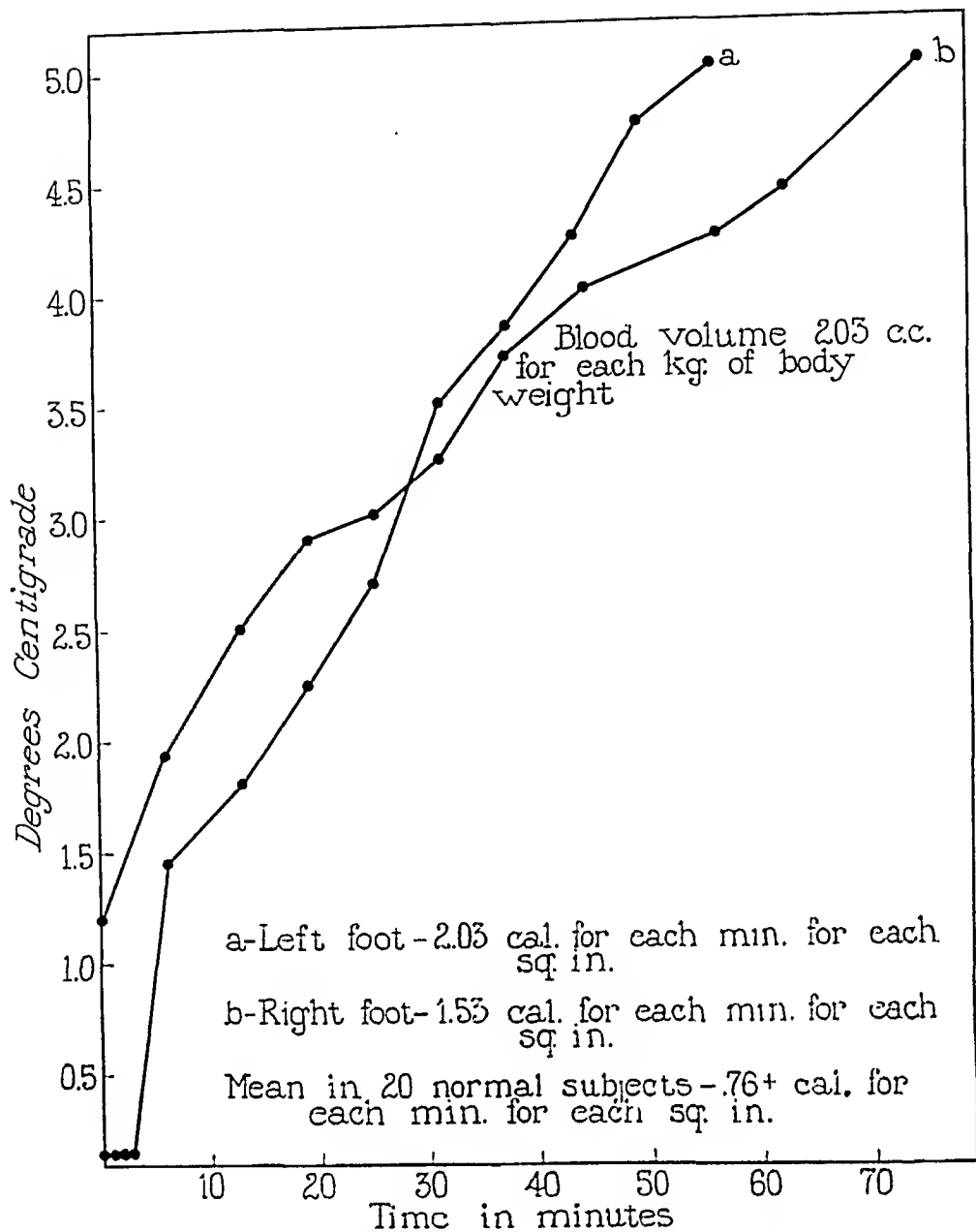


Fig. 5.—Rate of the elimination of heat as measured in small calories for each minute for each square inch of surface area. Sharp differences are shown in the right and left foot. The mean for normal subjects is given.

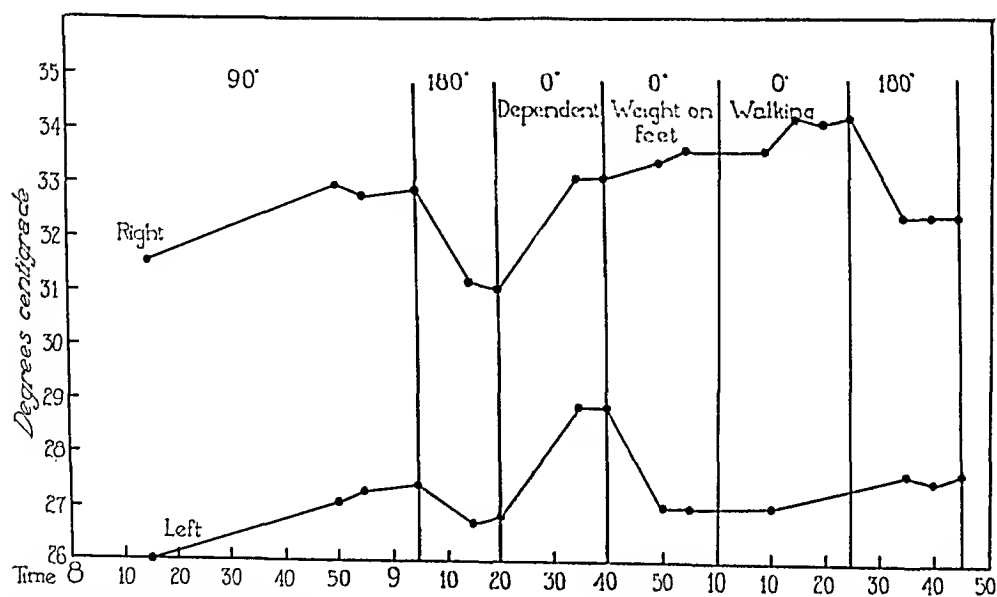


Fig. 6.—Effects of posture, weight bearing and walking on the surface temperature of the feet.

The cases of paresthesia associated with polycythemia vera are similar to those observed in older arteriosclerotic patients without polycythemia. The usual complaint is of a burning sensation in the feet, but not confined to the areas of pressure. Such cases should be distinguished from those in which there are predominant vasodilator disturbances. This can be done by means of measurements of the surface temperatures of the painful areas before and after exercise, and with different postures. In pseudo-erythromelalgia the temperature of the surface of the affected part is normal or low, although the patient states that the affected areas burn. Reduction of blood volume has less effect on the symptoms in the cases of simple paresthesia than in those with demonstrable vasodilator disturbances.

Cases of polycythemia vera, with painful vasodilator disturbances, are not unusual. Weber has described cases of this type. It is suspected, however, that Weber has confused the erythromelalgia of Mitchell with the rubor seen in cases of thrombo-angiitis obliterans and arteriosclerosis with occlusion of the arteries. It is not the color of the extremities that determines the diagnosis of erythromelalgia, but an increased volume and flow of blood through the extremities, accompanied by redness and distressing symptoms, and proved by an increased surface temperature during the attack. Erythromelalgia is an extremely rare condition. The diagnosis rests on the criteria first described by Mitchell; intermittent periods of vasodilatation of the extremities are associated with redness, burning hyperhidrosis and dilated, throbbing veins. In the cases described by Mitchell, the disturbances were symmetric and bilateral. Cases with unilateral disturbance have not been observed in our experience, except in association with polycythemia vera, and even in these cases vasodilatation was present in both feet, but was more marked and produced symptoms in one foot. All cases of erythromelalgia which have come under observation in recent years have been studied from the standpoint of the possible existence of polycythemia vera; in this way two cases have been detected. Spastic phenomena of the Raynaud type were present in three cases, and the reduction of blood volume effected complete relief.

Our endeavor to estimate the incidence of symptoms due to peripheral arterial disease in polycythemia vera is based largely on records; only recent cases have been studied in detail. The classification can be regarded as satisfactory, but the percentage of occurrence may later need to be revised.

BIBLIOGRAPHY

1. Peacock, H. A.: Blood Pressure and Blood Volume in Cases of Polycythemia Vera, *Proc. Staff Meet., Mayo Clin.* **4**:286 (Sept. 25) 1929.
2. Stewart, G. N.: Studies on the Circulation in Man: I. The Measurement of the Bloodflow in the Hands, *Heart* **3**:33 (Oct.) 1911.

COMMENT

The clinical analysis of this group of cases indicates that disease of the peripheral arteries is relatively common in polycythemia vera and that it may cause unusual symptoms and aberrant manifestations. The recognition of this fact makes one responsible for excluding polycythemia vera in all cases which present evidence of peripheral vascular disease. The cases with claudication, without demonstrable closure of the large arteries of the extremities, are of particular significance. Two factors probably are operative: 1. There is an organic factor resulting in narrowing of the lumen of the smaller arteries. 2. Anoxemia is caused by marked reduction in the rate of circulation. Direct observation of the flow of blood through the surface capillaries in cases of polycythemia vera demonstrates extreme sluggishness of flow. The capillary blood is close to the threshold of cyanosis, and moderate decreases in environmental temperature cause complete stasis of the blood in the loops, and produce cyanosis of the capillary blood. Recent studies have demonstrated similar retardation in the flow of blood in the larger vessels. The utilization of oxygen in the extremities of patients with polycythemia vera, as determined by the oxygen content of arterial and venous blood, is increased. Claudication, which is an expression of anoxemia, may be largely of a functional type. The supply of oxygen to muscle may be impaired by the increased viscosity of the blood and retardation of its flow, and perhaps organic changes in the walls of the capillaries prevent adequate exchange of oxygen. A correct diagnosis of the underlying condition is important because so frequently reduction in blood volume and viscosity results in symptomatic improvement and return to almost normal activity.

Only one case of occlusion of the arteries, with gross gangrene, was observed, and this occurred in an aged patient. This incidence is in marked contrast to the occurrence of venous occlusion.

The association of thrombo-angiitis obliterans with polycythemia vera is rare; the case reported here is the second in the literature. Weber described a similar case in a Jew, aged 43, the clinical description of which is satisfactory although pathologic proof was not obtained. One of us (Brown) has had the opportunity of observing a large number of cases of thrombo-angiitis obliterans in which studies have been made on the viscosity of the blood, the blood volume, and the concentration of erythrocytes and hemoglobin, and in no other case has polycythemia vera been encountered. This is of especial interest because it has been frequently suspected that changes in the blood are a factor in thrombo-angiitis obliterans, chiefly in the production of thrombosis; this hypothesis has led to the use of anticoagulants. There is no evidence, however, to indicate that this is true.

ACUTE · MONOCYTIC (HISTIOCYTIC) LEUKEMIA

REVIEW OF THE LITERATURE AND CASE REPORTS *

WILLIAM DAMESHEK, M.D.

BOSTON

The conception is still general that but two types of leukemia exist: myelogenous, arising from the bone-marrow, and lymphatic, arising from the lymphoid tissue. That there is a third form of leukemia, arising from the reticulo-endothelial (histiocytic) system and characterized hematologically by an extreme degree of monocytosis and histiocytosis, is not as yet well recognized. Comparison of the reported cases indicates their similarity and emphasizes the existence of a clearcut entity, monocytic leukemia. Reschad and Schilling-Torgau,¹ in 1913, were the first to describe this "new" form of leukemia. Since then twenty-six cases have been reported. The most complete studies have been made by Merklen and Wolf.² The present communication describes the observations in two additional cases.

REPORT OF CASES ³

CASE 1.—*History*.—M. R., a Jewish business man, aged 55, was admitted to the hospital on Oct. 21, 1928, complaining of swollen gums. The family and marital history were not significant. He had felt well until 1926, when several teeth were extracted because of abscess formation. In October, 1927, the right submaxillary gland was removed because of calculi in the duct. At that time he had felt slightly depressed and had noted occasional pain in the flanks, relieved by rest. During the summer of 1928, he suffered from pain at the left costal margin, particularly on taking a deep breath. One month before entry to the hospital, his gums became painful and swollen. He had consulted several dentists, and the diagnoses of Vincent's angina, pyorrhea and abscess formation were considered. Four lower teeth were extracted. The gums did not heal, and pain became severe. When the patient was finally admitted to the hospital he was unable to sleep and was markedly depressed.

Examination.—Physical examination showed a short, rather stocky man who was quite apprehensive. The buccal mucous membranes were slightly reddened

* Submitted for publication, March 10, 1930.

* From the Medical Department, Beth Israel Hospital.

1. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr. **60**:198 (Sept. 9) 1913.

2. Merklen, M., and Wolf, M.: Monocytes, monocytozes, leucémies à monocytes; trialisme leukocytaire, Presse méd. **35**:145 (Feb. 2) 1927; Leucémies à monocytes, Rev. de méd. **45**:154, 1928.

3. I am enabled to report the first case through the kindness of Dr. Harry Linenthal of the Beth Israel Hospital.

3. Kegerreis, Roy: Calorimetric Studies of the Extremities: II. Experimental Apparatus and Procedures, *J. Clin. Investigation* **3**:357 (Dec.) 1926.
4. Geisböck, Felix: Die Bedeutung der Blutdruckmessung für die Praxis, *Deutsches Arch. f. klin. Med.* **83**:363 (July) 1905.
5. Müller, L. R.: Studien über den Dermographismus und dessen diagnostische Bedeutung, *Deutsches Ztschr. f. Nervenhe.* **47-48**:413-434, 1913.
6. Cassirer, Richard: Die vasomotor-trophischen Neurosen, Berlin, S. Karger, 1912, pp. 144-181.
7. Brown, G. E., and Giffin, H. Z.: Studies of the Vascular Changes in Cases of Polycythemia Vera, *Am. J. M. Sc.* **171**:157, 1926.
8. Weber, F. P.: Polycythemia, Erythrocytosis and Erythraemia, New York, Paul B. Hoeber, Inc., 1922, p. 79.
9. Mitchell, S. W.: On a Rare Vaso-Motor Neurosis of the Extremities, and on the Maladies with Which It May Be Confounded, *Am. J. M. Sc.* **76**:2, 1878.

be drawn between the histiocytes and the monocytes. There was marked differentiation, however, between these cells and the polymorphonuclear cells and lymphocytes. These distinctions have been well described by Sabin and others.

The case rapidly resolved itself into one of acute leukemia. Because of the high white count, the marked monocytosis with the presence of many histiocytes, the fever and the hepatic and later splenic enlargement, the diagnosis of monocytic leukemia was made. Lymphatic leukemia could be ruled out because the lymphocytes were both relatively and absolutely decreased and because the type cell corresponded in no respect to the morphology of the lymphocyte. Myelogenous leukemia could also be ruled out because of the following considerations: relative and absolute diminution in the granular or myeloid cells, almost complete absence of myeloblasts, scarcity of myelocytes and rarity of eosinophils and basophils. There was only one other conclusion, that this was a case of monocytic leukemia.

The remainder of the clinical course of the case, with laboratory data, is given in table 1.

CASE 2.—History.—J. D., a cobbler, about 70 years of age, was admitted to the Beth Israel Hospital, on May 17, 1930. There was nothing of consequence in the familial or past history. He was well until nine weeks before admission, when he tripped and fell down a flight of stairs, bruising his left leg. The leg became greatly swollen and painful, and there was pain in the lower part of the back. The pain gradually subsided, but four weeks before admission, a severe chill developed, followed by a temperature of 105 F. Fever had been present since that time. A week later, there was pain in the right flank, associated with frequency and urgency of urination. Two weeks before admission the right side of his throat became painful; at this time swollen glands were noted under the right jaw, and clinical signs of frontal sinusitis were present. The patient grew progressively weaker and paler, and lost 34 pounds (15.4 Kg.) during his nine weeks of illness. Examination on entrance disclosed an obviously sick man with marked pallor. Positive observations were: tenderness over the right frontal sinus, large tonsils and bean-sized lymph nodes at the angles of both jaws and in both supraclavicular fossae. No other lymph nodes could be felt, nor were the spleen and liver palpable. No petechiae were present.

Roentgenograms of the sinuses disclosed involvement of the right frontal, right ethmoid and right antrum; the spine showed callous formation at the anterior portion of the third thoracic vertebra, probably due to a fairly recent fracture. The Wassermann reaction and culture of the blood were negative.

The blood picture on admission was unusual; only 5.6 per cent of polymorphonuclear cells were present, there being a lymphocytosis and monocytosis with what were at first considered to be lymphoblasts. The latter, however, were soon found to be oxidase-positive, and were therefore called myeloblasts. As will be shown in table 2, there was at first an increase in the myeloblasts, followed, however, by a rapid recession; the monocyte percentage rapidly rose from 29.6 per cent on admission to 86.8 per cent on the day of death. Typical histiocytes in large numbers were seen on May 20; thereafter most of the cells appeared to be typical monocytes, though the cells were somewhat larger than the ordinary monocyte, the nucleus often being more round or oval, and without indentation. The ordinary monocyte took the oxidase stain faintly, a small number of fine granules being present; the histiocyte was always oxidase-negative, however. On May 21, 22 and 23, although by Wright's stain the percentage of mature or ordinary monocytes far exceeded that of the histiocytes, oxidase stain showed that the great majority

and swollen. The gums of the lower teeth were much inflamed, edematous, tender and spongy. The gums of the upper teeth showed similar, though not so marked, changes. Many of the lower teeth were missing. The tonsils, of moderate size, were apparently not diseased. A scar was present over the right submaxillary region. The heart and lungs were normal. The liver was definitely enlarged, its upper border being at the fifth rib and its lower border being felt threefinger breadths below the right costal margin. The spleen was not palpable. The skin showed slight pallor; there was no icterus or petechial spots. There was no apparent enlargement of the lymph nodes. The reflexes were normal. The temperature was 100 F., and the pulse rate, 100 per minute.

Laboratory Data.—Blood studies done as a routine gave striking observations: hemoglobin (Tallqvist), 70 per cent; red blood cell count, 4,500,000 per cubic millimeter; white blood cell count, 31,200. The differential count of the white blood cells showed: polymorphonuclear cells, 21.5 per cent (19 per cent mature, 2 per cent metamyelocytes, 0.5 per cent myelocytes); eosinophils, 0.5 per cent; lymphocytes, 12.5 per cent; monocytes, 65.5 per cent.

The monocytes were of two distinct types. The first type was the ordinary large mononuclear cell of the blood stream, from 12 to 18 microns in diameter, with grayish-blue cytoplasm containing innumerable, very fine azure granules; the nucleus was usually bean-shaped and was composed of a fine reticulum without nucleoli. The second type of monocyte was apparently the "type cell" of this blood picture. This was a very large, round or polygonal cell from 20 to 50 microns in diameter. Its cytoplasm was weakly basophilic. The cell boundaries were indistinct and irregular and pseudopods, or budding of the cytoplasm, were common. There were many granules, rather coarser and redder than in the ordinary monocyte and almost always grouped about the nucleus, hardly ever in the periphery of the cell or in the pseudopods. This peculiar distribution gave the cell a distinctive appearance. The nucleus was violet (Wright's stain), round or oval and "spongy." In color, form, size, distribution of granules, shape, size and character of nucleus, the cell was typical of the hemohistioblast of Ferrata⁴ and of the histiocyte of other authors. Cells intermediate between the typical histiocyte and the typical monocyte could be seen.

Oxidase staining of the blood smear by the method of Sato and Yoshimatsu⁵ showed the ordinary monocytes to be oxidase-positive, the granules being very fine, more sparse and less blue than in the polymorphonuclear cells. The immature monocytes or histiocytes were oxidase-negative. Supravital staining of the blood was done by the method of Sabin⁶ and showed the large cells to be extremely active. At 37.5 C. their ameboid motion was very striking. There was continual alteration in both the size and the shape of the cells. Long streamers or pseudopods were constantly being sent out; these were seen to be wholly without granules. If the pseudopod remained stationary for a short time, a few granules would appear in it. One cell was seen with a red blood cell inclusion; the frequent and marked changes in size and shape of this cell were striking. The ordinary monocyte was not so active, and there was typical clustering of neutral red granules in the bend of the nucleus. However, no clear dividing line could

4. Ferrata, A.: *Le emopatie*, Milano, Societa Editrice Libreria, 1918.

5. Sato, A., and Yoshimatsu, S.: The Peroxidase Reaction in Epidemic Encephalitis, *Am. J. Dis. Child.* **29**:301 (March) 1925.

6. Sabin, F. R.: Studies of Living Human Blood Cells, *Bull. Johns Hopkins Hosp.* **34**:277, 1923.

of the monocytes was oxidase-negative, in spite of the fact that with Wright's stain large numbers of lilac-staining granules were present in the cytoplasm.

Supravital smears were made daily and showed large numbers of histiocytes and monocytes identically as described in the first case.

Biopsy of the bone-marrow (sternum) was made on May 20. Smears and sections were examined and showed marked crowding of the marrow with primitive cells; 76 per cent of these were oxidase-negative, 1.7 per cent oxidase doubtful and 22.3 per cent oxidase-positive. The oxidase-positive cells included 21.3 per cent of myeloblasts, 0.3 per cent of polymorphonuclear cells and 0.7 per cent of myelocytes. Most of the oxidase-negative cells, which were extremely large, were seen by Wright's stain to be the typical hemohistioblasts of Ferrata with a characteristic spongy nucleus and irregular pale blue-staining cytoplasm.

TABLE 2.—*Blood Picture of Patient in Case 2*

	5/18/30	5/19/30	5/20	5/21	5/22	5/23 a.m.	5/23 p.m.
Hemoglobin.....	55			44			
Red blood cells.....	3,720,000	3,670,000		2,800,000			
Platelets.....		148,000					
Reticuloocytes.....		0.2					
White blood cells.....	17,200	13,300		21,700	51,800	68,800	124,000
Polymorphonuelears.....	15.6	33.0	27.5	22.5	11.2	6.0	
Mature.....	4.0	4.5	2.5	5.0	1.6	2.0	
Band.....	1.6	1.5	2.0	3.5	2.4	1.2	
Young.....							
Myelocytes.....							
Promyelocytes.....							
Myeloblasts.....	10.0	27.0	23.0	14.0	7.2	2.8	
Lymphocytes.....	54.8	47.5	28.0	23.5	4.4	7.2	
Small.....	32.4	22.0	4.0				
Large.....	20.4	25.0	24.0				
Plasma.....		0.5					
Rieder.....	2.0						
Monocytes.....	29.6	19.5	44.5	54.0	84.4	86.8	
Ordinary.....	29.6	19.0	25.0	45.0	77.6	86.4	
Histiocytes.....		0.5	19.5	9.0	6.8	0.4	

In view of the rapid course, the blood picture and the extreme crowding of the bone-marrow with primitive cells, the diagnosis of acute leukemia was justified. The absence of myelocytes, the constantly increasing number of monocytes and histiocytes (checked by supravital and oxidase staining), the observations in the biopsy of the bone-marrow all served to establish the diagnosis of monocytic (histiocytic) leukemia as against that of myelogenous leukemia.

The patient became rapidly worse. The temperature rose to 105 F., and on May 23, six days after admission, and about ten weeks after the onset of the illness, he died. Permission for autopsy was not obtained; however, bits of muscle and bone-marrow from the sternum were procured. The sections showed crowding of the blood vessels with large mononuclear cells, with some infiltration into the skin and muscle tissue. Bone-marrow showed almost the same observations as in the biopsy specimen, except that more histiocytes and fewer myeloblasts were present.

TABLE 1.—Clinical Course and Laboratory Data in Case 1

Date	Clinical Signs and Symptoms; Treatment	Tem- pera- ture	Hemo- globin (Sahli), per Cent	Red Blood Cell Count	White Blood Cell Count	Poly- morpho- nuclear Cells, per Cent	Mature, per Cent	Meta- myelo- cytes, per Cent	Myclo- cytes, per Cent	Lym- pho- cytes, per Cent	Mono- cytes, per Cent	Mature, per Cent	Histio- cytes, per Cent	Eosino- phils, per Cent	Baso- phils, per Cent
10/24/28	Blood cultures negative; pain lower left side of chest; sweating	98-101 F.	72,600
10/26/28	Dr. George R. Minot felt spleen 6 cm. below costal margin; roentgen therapy to upper midchest
10/27/28	Roentgen therapy begun over spleen	60	3,105,000	36,800	23.0	21.0	2.0	...	21.0	56.0	24.0	22.0
10/29/28	52	19,200	4.0
11/ 2/28	Pains in various joints; roentgen therapy over spleen	52	3,040,000	30,800	14.0	13.5	0.5	...	25.5	60.0	6.5	53.5	..	0.5
11/ 5/28	54	2,830,000	32,400
11/ 9/28	Roentgen therapy over spleen...	52	54,200	51.0	27.0	20.5	19.5	1.0	1.0	0.5
11/12/28	Many Vincent's organisms found below the gums; neocarsphenamine given intravenously	52	2,740,000	48,800	35.5	21.5	41.5	8.5	33.0
11/16/28	Roentgen therapy over the gums with slight improvement
11/19/28	Roentgen therapy over jaws (gums)	50	2,560,000	37,600	39.5	2	17.5	41.5	9.5	32.0
11/21/28	23.0	21.5	2.0	...	7.5	68.0	8.0	60.0
11/23/28	Slight swelling and marked tenderness over anterior surface of right ankle joint; slight tenderness over lower ribs on left side; roentgen therapy over ribs and anterior spleen
11/26/28	Vague pains; x-ray films of long bones negative
11/27/28	Vital staining studies confirmed previous studies; sore throat; marked swelling of one of cervical lymph nodes; thrombosis of one of cubital veins; blotchy eruption appeared	87,400	19.5	14.5	5.0	...	7.0	73.5	9.5	70.0
11/30/28	Intense itching over body; Dr. J. Swartz considered rash to be leukemic infiltration of skin	23	2,350,000	147,400	29.0	26.0	3.0	...	2.0	69.0	3.0	66.0
12/ 4/28	24	1,440,000	18.0	15.0	3.0	...	3.5	78.5	7.5	4.0
12/12/28	Face edematous; patient slightly irrational	16	1,010,000	88,400
12/14/28	Death after stupor; autopsy not obtained

TABLE 3.—*Review of the Literature*

Author	Date of Case Report	Sex	Age	Duration of Disease	White Blood Cells	Percentage of Monocytes	Postmortem Observations and Comment
Reschad and Schilling-Torgau: München. med. Wehnschr. 60: 198 (Sept. 9) 1913	1913	M	33	8½ weeks	15,000 to 36,000	72 to 74	Infiltration of skin, bone-marrow, spleen and liver with large mononuclear cells
Fleischmann: Folia haemat. 20: 19, 1915.....	1915	M	47	6 months	15,600 to 36,000	65 to 58	Infiltration of spleen, lymph nodes, bone-marrow and liver with very large "endothelial" cells; myelocytes also present
Bingel: Deutsche med. Wehnschr. 42: 1503, 1916..	1916	M	48	9 weeks	4,500 to 16,500	44	Splenic pulp filled with large oxidase-negative cells, not lymphocytes
Rosenthal: M. Clin. North America 4: 1607, 1921..	1921 (1)	M	5	?	245,000	87.4	
	(2)	Not described					
	(3)	M	34	4 months	660 to 3,000	44	Liver infiltrated with large numbers of mononuclear cells
Komiya and Hayashi: Mitt. a. d. med. Fakult. d. K. Univ. zu Tokyo 27: 375, 1921	1921	M	20	5 months	102,000 to 326,000	65 to 79	Intense infiltration of the bone-marrow, splenic pulp, lymph nodes and liver with large mononuclear cells oxidase-negative
Ewald, Freilse and Hennig: Deutsches Arch. f. Klin. Med. 138: 353, 1922	1922 (1)	M	32	24 days	140,000	80 to 87 "Stammzellen" 4.5 to 8	Intense infiltration with large cells ("Stammzellen")
	(2)	M	30	6 weeks	99,000	5 to 7 "Lymphoidocytes" 90	Infiltration with "lymphoidocytes" which were oxidase-positive
	(3)	F	29	?	56,000	60 "Stammzellen" 24	Infiltration with "Stammzellen" and myelocytes
Reitano: Haematologica 3: 524, 1922.....	1922	Blood smears of two cases studied; one of Alder (Folia haemat. 29: 105, 1923); one of Castellino and Ferrata (1914); predominating cells: monocytes and hemohistioblasts of Ferrata

N/6

N/0

The following cases of acute monocytic leukemia have been described thus far:⁸

Reschad and Schilling-Torgau.....	1913	1 case
Fleischmann	1915	1 case
Bingel	1916	1 case
Rosenthal	1921	3 cases
Komiya and Hayishi.....	1921	1 case
— Ewald, Frehse and Hennig.....	1922	3 cases — ?
— Reitano	1922	1 case — ?
— Ferrata and Reitano.....	1923	1 case — ?
Alder	1923	3 cases
— Naegeli	1923	3 cases — ?
— Hoff	1926	1 case — ?
Merklen and Wolf.....	1927	1 case
Ugriumov	1928	1 case
Hannema	1928	1 case
Schwirtschewskaja	1928	1 case
Hittmair	1928	1 case
Wyschegorodzowa	1929	1 case

In addition, Merklen and Wolf² classed as cases of monocytic leukemia those described by the following authors: Hindenburg (1895), Hertz and Kino (1910), Lino (1924) and Bonnel and Fauqué (1928). Wyschegorodzowa⁹ cited a case reported by Barantschik. The case of Hindenburg seems to fit into this group, but Hertz and Kino's case seems to be myeloblastic. The latter three cases could not be checked.

This gives a total of twenty-nine cases, making thirty-one with the present cases. The diagnosis of monocytic leukemia is to be questioned in the following cases: the three cases of Ewald, Frehse and Hennig, which may be cases of myelogenous leukemia with myeloblasts and premyelocytes; the three cases of Naegeli, which are shown by the author himself to be myelogenous leukemia; Hoff's case, which is perhaps one of agranulocytosis, and three of the four cases cited by Merklen and Wolf as monocytic, i. e., those of Hertz and Kino, Lino, and Bonnel and Fauqué. The evidence that these are cases of monocytic leukemia is not entirely conclusive. In addition, the cases of Reitano and of Ferrata and Reitano are not described fully, the reports taking up mainly the morphologic descriptions of the cells. Barantschik's case could not be found. This brings the total of well substantiated, fully described cases of acute monocytic leukemia to eighteen, including the present cases.

8. These cases are reviewed in this article.

9. Wyschegorodzowa, W. D.: Zur Frage der monozytären Leukämie, *Folia haemat.* **38**:355 (July) 1929.

Alder: Folia haemat. 29: 105, 1923.....	1923	M	30	Few weeks	100,000	"Granular cells" 40.5	Diagnosis "acute leukemia with marked proliferation and granulation (monoblastic-monocyte leukemia)"
	case 7						
	case 8	M	78	3 months	8,000 to 46,000	"Indented forms" 36.5 "Granular cells" 8.0	Diagnosis "acute leukemia with nuclear polymorphy and granulation (monocyte leukemia)"
	case 12	F	52	14 days	80,000 to 400,000	"Granular cells" 70.0	Diagnosis "myeloblastic leukemia with abnormal nuclear proliferation and cells with fine granulation (monocyte leukemia)"
Ewald: Leukämische Retikuloendotheliose, Deutsches Arch. f. klin. Med. 142: 222, 1923	1923	M	60	?	15,000	Monocytes 0.2 "Pathologische Stammzellen" 94.75	Infiltration of spleen and bone-marrow with very large cells which contained pseudopods and were intimately associated with the reticulum
Naegeli: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923	1923 (1)	69.1	Pus in right midlung with rupture into pericardium
	(2)	12.2 and 1.3	Diagnosis "acute myelogenous leukemia with many monocytes"; myeloid infiltration
	(3)	M	50	4,000	60	Myeloid proliferation in liver, spleen and bone-marrow
Ferrata and Reitano: Haematologia 4: 35, 1923	1923	Not described					Spleen showed marked increase in monocytes
Hoff: Virchows Arch. f. path. Anat. 261: 142, 1926 case 4	1926	M	41	3 weeks	2,500 to 5,000	15 to 45	Diffuse infiltration of the reticular tissue in lymph nodes, spleen and bone-marrow (see chapter on pathology)
Merklen and Wolf 2.....1927, 1928	1927, 1928	M	30	3 months	20,000 to 43,000	Monocytes and monoblasts 71 "Ferrata" cells 14	See chapter on pathology
Ugrumov: Akuter Retikuloendotheliose, Zentralbl. f. allg. Path. u. path. Anat. 42: 103, 1928	1928	M	30	23 days	36,000	46.5	Intense infiltration of liver, splenic pulp and lymph nodes
Hannema: Nederl. tijdschr. v. geneesk. 1: 2281, 1928 1928	1928	M	11	19 days	107,000	81	See chapter on pathology
Schwirtschewskaja: Leukämische retikuloendotheliose, Virchows Arch. f. path. Anat. 267: 456, 1928	1928	M	27	2½ months	6,630	58.7 to 83.3 (many monoblasts)	Liver capillaries and splenic pulp filled with large cells, oxidase-positive
Hittmair: Folia haemat. 37: 321, 1928.....	1928	M	63	1 week	33,200	82.7	Infiltration of bone-marrow, spleen, lymph nodes and skin with large mononuclear cells; in the spleen, reticular cells swollen, often with pseudopods, often lying free and containing phagocytosed particles and red blood cells; Kupffer's cells swollen
Wyschegorodzowa: Folia haemat. 38: 355, 1929.....1929	1929	F	38	5 months	2,000 to 23,000	74.5	

"aleukemic" (Rosenthal,¹⁵ case 2; Schwirtschewskaja,¹⁶ at onset). The average white blood cell count seems to be somewhat lower than in the other two types of acute leukemia, ranging usually from 15,000 to 45,000 per cubic millimeter. Occasionally the white blood cell count reaches very high limits, being 400,000 in one of Alder's cases.¹⁰

The differential count of the white blood cells ranks first in diagnostic significance. Instead of a marked increase in myelocytes, myeloblasts, lymphocytes or lymphoblasts, there is a marked preponderance (usually from 70 to 90 per cent) of large cells. These are of two varieties: The first type is the ordinary monocyte seen in normal blood pictures. The second type, which is found in greater and greater numbers as the

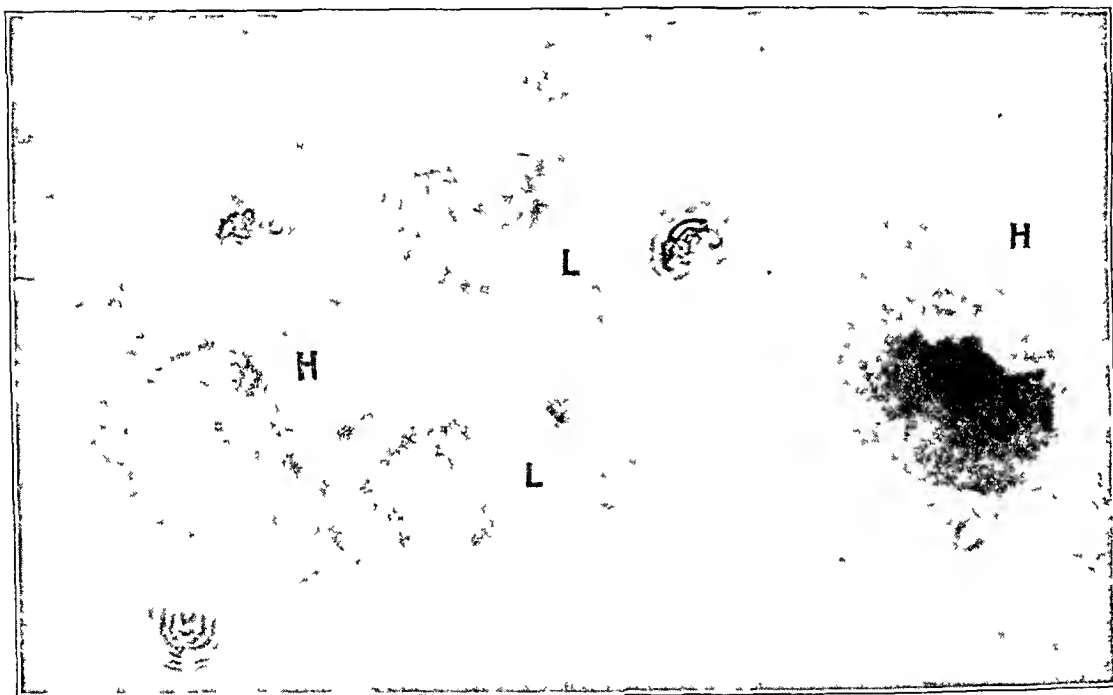


Fig 2—Photomicrograph, oil immersion lens, $\times 1,500$; Wright's stain, Oct 24, 1929. Two histiocytes (H) and two lymphocytes (L) are shown. Note the faint pseudopods projecting from the histiocyte on the left.

disease progresses, is the histiocyte, the probable forerunner of the monocyte. By Merklen and Wolf,² these cells are called monoblasts; by Ferrata and Reitano,¹⁷ hemohistioblasts; by Sabin,¹⁸ clasmatoctes.

15. Rosenthal, N.: Some Atypical Cases of Leukemia, *M. Clin North America* 4:1607 (March) 1921.

16. Schwirtschewskaja, B.: Ueber leukamische Retikuloendotheliose, *Virchows Arch. f. path. Anat.* 267:456, 1928.

17. Ferrata, A., and Reitano, D.: Sindromi istiocitemiche (emoistoblastische), *Haematologica* 4:385, 1923.

18. Sabin, F.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, *Carnegie Inst. Contrib. Embryol.* 16:125, 1925.

ANALYSIS OF THE CASES

Clinical Symptoms.—In general, acute monocytic leukemia differs clinically but slightly from the other acute leukemias. The cases occur almost entirely in males, only two (Alder's¹⁰ no. 12 and Wyschegorod-zowa's⁹ case) occurring in women. The condition appears at any age, from 5 to 78, most of the cases occurring in the age group from 30 to 50.

Etiology.—The etiology is wholly unknown, as in the other leukemias, but several observers have expressed the opinion that the disease is an infection. This opinion is strengthened by the fever, rapid course and almost invariable gingivitis. Some observers, notably Sternberg¹¹ and Krahn,¹² feel quite strongly that these cases are infections, sufficient irritation of the reticulo-endothelial system having taken place to cause a marked monocytosis. This, to be sure, does not explain the proliferative character of the lesions and the 100 per cent mortality. Blood cultures have been taken in several cases, with negative results.

Onset.—The onset is gradual, usually with fatigue or swollen gums, but at times is acute, with high fever (Ugriumov;¹³ Hannema;¹⁴ Alder,¹⁰ case 12). The disease progresses fairly rapidly when the first symptoms appear; the gums become more and more swollen, often ulcerate and at times become gangrenous; fever becomes sustained, and pallor develops. At the first examination, pallor is usually pronounced. The gums are found to be necrotic and swollen. There may or may not be slight glandular enlargement. The liver is usually slightly enlarged, and the spleen is almost always felt below the costal margin. Petechial spots are common, and bleeding is often pronounced. The disease lasts from two weeks to six months, ten weeks being the average time; death occurs either in coma or after repeated bleeding.

Diagnosis.—The diagnosis is made only by morphologic examination of the blood. This shows some degree of secondary anemia, usually marked, the hemoglobin becoming as low as 14 per cent, and the red blood cell count as low as 900,000 per cubic millimeter. The white blood cell count is almost always elevated, though an occasional case is

10. Alder, A.: Ueber abnorme Zellformen und ihre Häufigkeit bei akuter Myelose, *Folia haemat.* **29**:105 (July) 1923.

11. Sternberg, C.: Akute Leukämie, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 1, p. 76.

12. Krahn, H.: Retikuloendotheliale Reaktion oder "Retikuloendotheliose" (3. Leukämieform?), *Deutsches Arch. f. klin. Med.* **152**:179 (Aug.) 1926.

13. Ugriumov, B.: Ein Fall von akuter Retikuloendotheliose, *Zentralbl. f. allg. Path. u. path. Anat.* **42**:103, 1928.

14. Hannema, L. S.: Geval van monocysten leucämie, *Nederl. tijdschr. v. geneesk.* **1**:2281 (May 5) 1928.

also in the bone-marrow and usually in the sinusoids of the liver. Most interesting descriptions showing the direct association between the proliferative reticulo-endothelial cells and the leukemic cells are given by several authors. Ewald described the splenic pulp as filled with large cells, the nuclei being slightly indented; pseudopods, apparently associated with the reticulum cells, were frequently seen. Ugriumov described the mesenteric lymph nodes as markedly enlarged and reddened, the spleen and liver being much enlarged. The splenic pulp and

TABLE 4.—*Differentiating Points Between the Cells*

	Monocyte	Large Lymphocyte	Mycloblast	Premye-locyte	Polymorpho-nuclear
Size.....	10-20 microns	10-15 microns	6-15 microns	10-20 microns	10-15 microns
Shape.....	Oval	Elongated oval	Round to oval	Round to oval	Round
Pseudopods...	Fairly common	Rare	Little tags at times	None	None
Cytoplasm: Color.....	Grayish-blue*	Sky-blue	Ultramarine blue	Ultramarine blue verging to pink	Pink
Granules.....	Innumerable; very fine; azure	Large, azure in 10% of cells	Absent	Few, large, blue, red or violet	Many, large, blue, red or violet
Vacuoles.....	Rare	None	None	None	None
Nucleus: Size.....	Relatively large	Eccentric, $\frac{1}{2}$ size of cell	Fills almost entire cell	Large	Variable
Shape.....	Usually reniform*	Usually round	Oval, at times, indented	Round	Polymorphous
Size of chromatin.....	Fine network*	Thick, block-like masses	Extremely fine meshwork	Coarse, linear	Coarse, linear
Nucleoli.....	Absent*	Absent	1 to 5 in each cell	Occasional	None
Oxidase reaction	Slightly positive*	Negative	Usually positive	Positive	Positive
Vital staining...	Pseudopods, active movement*	Nucleus moves, rest of cell does not	No motion	No motion	Granules move and push cell membrane out

* The asterisk marks the most important factors in the differentiation.

liver capillaries were full of the large mononuclear cells. The Kupffer or stellate cells of the liver capillaries seemed to be increased in number and often contained red blood cells. The bone-marrow showed these cells in islands. Schwirtschewskaja described the sinuses of the splenic pulp distended with these large cells. In many places the endothelial cells were seen to project out into the lumina of the blood vessels. Pseudopods were common. The reticulo-endothelial system in the spleen, lymph nodes, bone-marrow and liver showed marked hyperplasia. Merklen and Wolf described a diffuse proliferation of the reticular tissue of the lymph nodes, spleen and bone-marrow. The splenic sinusoids showed hyperplasia of the endothelial tissue, and

Maximow¹⁹ finally adopted the term histiocyte, after having called them "resting-wandering cells" for years. A description of these cells will be found in the case report.

The diagnosis of monocytic leukemia rests clinically on the correct diagnosis of the cell known as the monocyte (the endothelial leukocyte of Mallory;²⁰ the large mononuclear cell of the older authors; the transitional cell of Ehrlich²¹). The diagnosis is ordinarily made without difficulty in a stained preparation. The oxidase reaction is helpful in certain cases as a means of differentiating these cells from lymphocytes and from the myeloid cells.

Supravital staining gives clearcut differentiating points. The monocyte is to be distinguished from the large lymphocyte, the myeloblast, the premyelocyte (and at times the myelocyte) and the polymorphonuclear cell. For convenience, the differentiating points were grouped in tabular form (table 4), the starred items representing the most important factors.

In considering the differential diagnosis, one must separate these cases from acute infections with monocytosis, from acute leukemias of other types and from agranulocytosis. Obviously the progress of the condition and the appearance of large numbers of histiocytes will in time separate the case from one of benign monocytosis. The differential diagnosis from acute leukemias of other types must be made by considering carefully the cell type from the criteria outlined. To differentiate from agranulocytosis becomes at times difficult if the case is of the "aleukemic" variety. The typical picture of agranulocytosis is easy to recognize, but those cases in which symptoms are prolonged may well be difficult to separate from monocytic leukemia. The absolute number of monocytes is to be considered, and histiocytes are to be searched for. In monocytic leukemia there is never complete disappearance of granular cells, whereas in agranulocytosis this is almost always the rule.

PATHOLOGY

Descriptions of postmortem examinations in the foregoing cases of monocytic leukemia are given in eleven instances. The most detailed descriptions are given by Ewald, Ugriumov, Schwirtschewskaja, Wyschegorodzowa and Merklen and Wolf. The lymph nodes, spleen and liver are always slightly enlarged. The normal architecture of the lymph nodes and spleen is effaced by the intense proliferation and infiltration of large mononuclear cells. There is marked infiltration

19. Maximow, A.: Les relations des cellules sanguines avec le tissu conjonctif et avec l'endothélium, *Ann. d'anat. path.* 4:701, 1927.

20. Mallory, F. B.: *Principles of Pathologic Histology*, Philadelphia, W. B. Saunders Company, 1923.

21. Ehrlich, P., and Lazarus, A.: *Die Anaemie*, Vienna, Alfred Hölder, 1909.

with lithium carmine, and by Goldmann,²⁸ in 1909, working with pyrrhol blue, that these histioid cells had the power of taking up dyes and other substances. This work was carried on by Tschachin,²⁹ who used various dyes, and was finally consummated by the most complete work of Aschoff and Kiyono,²⁶ in 1914. Kiyono³⁰ carried on this work in his own laboratory in Japan.

By the use of these dyes, it was possible to pick out a group or "system" of cells which had been shown before to be alike morphologi-

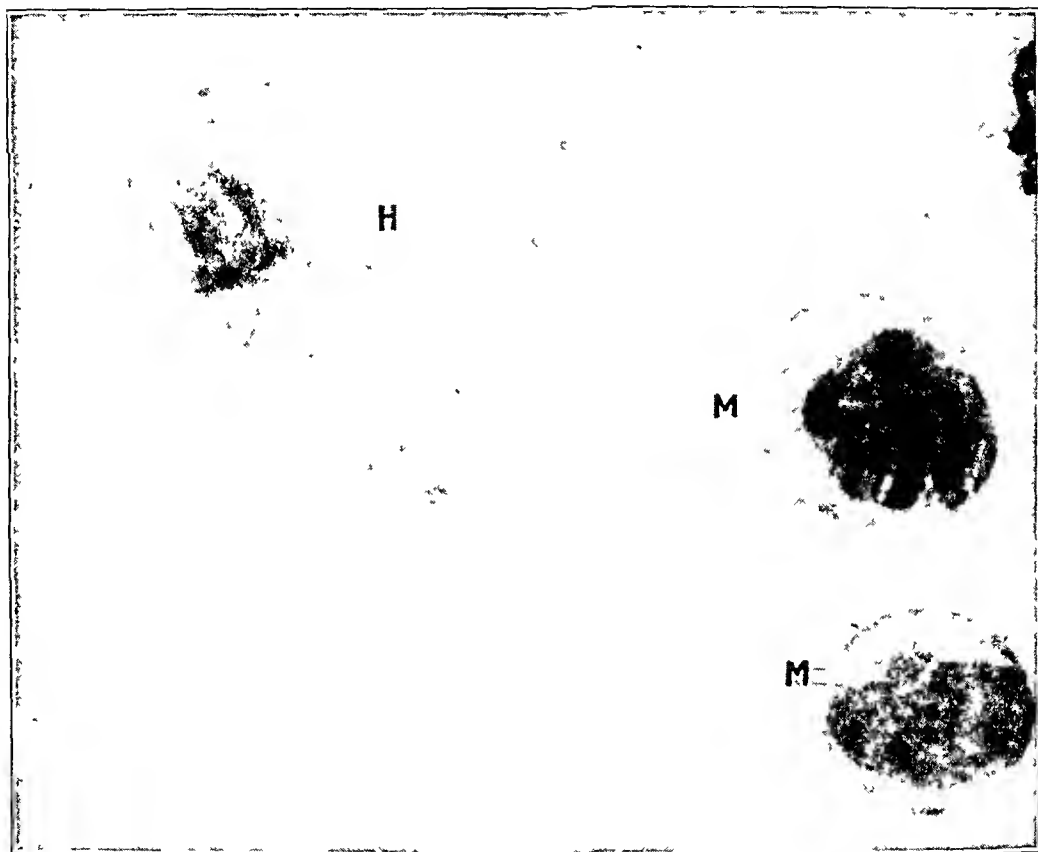


Fig. 3—Photomicrograph; oil immersion lens; $\times 1,500$; Wright's stain. The cell on the left is a typical histiocyte (*H*) with spongy nucleus and a pseudopod. The two cells on the right represent probably young monocytes (*M*), the nucleus being not yet indented.

28. Goldmann, E. E.: Die aussere und innere Sekretion des gesunden und kranken Organismus im Lichte der "vitalen Färbung," Beitr. z klin. Chir. **64**:192, 1909.

29. Tschachin, S.: Ueber die "ruhenden Wanderzellen" und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphozyten, Folia haemat. **17**:318, 1913.

30. Kiyono, K., and Nakanoin, T.: Weitere Untersuchungen über die histiocyten Zellen, Acta scholae med univ. imp. Kioto **3**:55, 1919-1920.

there was a monocytoïd metaplasia' of the bone-marrow. The Kupffer cells of the liver showed nothing abnormal. There is thus seen to be constant infiltration of the spleen, lymph nodes, bone-marrow and liver and at times direct evidences of proliferation of the reticulo-endothelial system. This system bears further description.

THE RETICULO-ENDOTHELIAL SYSTEM

A vast literature on the reticulo-endothelial system has accumulated, especially in the last few years. For the most complete reviews, the reader is referred to the articles of Maximow¹⁹ and Bloom²² and to the "Handbuch der Krankheiten des Blutes und der blutbildenden Organe," volume 2, articles by Aschoff and Schittenhelm.

Suffice it to say that scattered over the body in various organs and in intimate association with fibroblasts are certain large cells. In 1899, Ranvier²³ described these tissue cells as clasmatoocytes; Evans²⁴ termed them macrophages; Maximow,²⁵ in 1906, called them resting-wandering cells, but felt, in 1927,¹⁹ that Kiyono's²⁶ term "histiocyte," though not descriptive, was short and to be preferred, because it had been universally adopted. These histiocytes were to be found scattered in the stroma of the lymph nodes, bone-marrow, spleen and intestine and lining the sinusoids of the spleen, liver, lymph nodes and bone-marrow. In the stroma they seemed to form a reticulum or network and were therefore called "reticular" cells; if they lined the sinusoids, they were called "endothelial" cells. (Maximow objected to the latter, because he felt that it was the same cell whether it helped to form a reticulum or to line a blood vessel. He felt that real endothelial cells were completely differentiated and did not have hematopoietic powers at any time.)

These cells were characterized by certain functional properties: they might under the appropriate stimulus act as hemocytoblasts and thus give rise to other cells; under the influence of certain irritations, they might mobilize and be transformed to free cells which were very phagocytic. These phagocytic qualities could not be regarded as evidence of their inclusion in a "system." However, on the introduction of vital dyes by Ehrlich, it was found by Ribbert,²⁷ in 1904, working

22. Bloom, W.: The Origin and Nature of the Monocyte, *Folia haemat.* **37**:1 (Oct.) 1928.

23. Ranvier, L.: Des clasmatoocytes, *Arch. d'anat. micr.* **3**:123, 1899.

24. Evans, H. M.: The Macrophages of Mammals, *Am. J. Physiol.* **37**:243, 1915.

25. Maximow, A.: Untersuchungen über Blut und Bindegewebe, *Arch. f. mikr. Anat.* **73**:444, 1909.

26. Kiyono, K.: Die vitale Karminspeicherung, Jena, Gustav Fischer, 1914.

27. Ribbert, H.: Die Abscheidung intravenös injizierten gelösten Karmins in den Geweben, *Ztschr. f. allg. Physiol.* **4**:201, 1904.

theliosis (Letterer,⁴⁰ Goldschmidt and Isaac,⁴¹ Sachs and Wohlwill⁴²). Epstein⁴³ preferred to group all these cases under the title of "histiocytomatoses." He subclassified these into the following types: storage (Gaucher's disease, Niemann's disease, xanthomatosis); infectious proliferative (granulomas) Hodgkin's disease; hyperplastic—aleukemic, leukemic; dysplastic—tumors (reticuloma, endothelioma).

Morphologically, culturally, functionally and pathologically, it can be shown that scattered throughout the body, especially in various organs, are certain large cells, the histiocytes, which can be grouped into one system, the reticulo-endothelium. An acute irreversible proliferation of that system gives the clinical picture called monocytic leukemia.

THE MONOCYTE

It is on the basis that the monocyte is derived directly from the histiocytes composing the reticulo-endothelial system that the conception of monocytic leukemia as a third type of leukemia rests. Almost all are agreed that there are three types of white blood cells, the granular or myeloid, the lymphoid and the monocytic. Since there are these three types of white blood cells, there may be and are three types of leukemias—so Schilling, Rosenthal and other writers on the subject have argued. Some authors have refused to give the monocyte a position independent from the lymphocyte (Weidenreich,⁴⁴ Patella,⁴⁵ Bloom²²). Naegeli⁴⁶ stands alone in saying that they are bone-marrow cells.

The "monocyte question" is one that occupies a leading place in hematologic discussion. Maximow has long been known as a "unitarian" on the subject, believing that all white blood cells are derived, as has been shown, from the same cell—the hemocytoblast. In his later years, Maximow¹⁹ admitted that in the circulating blood of the normal adult, the monocytes seemed unique, and he therefore felt they

40. Letterer, E.: Aleukämische Retikuloze, Frankfurt. Ztschr. f. Path. **30**: 377, 1924.

41. Goldschmidt, E., and Isaac, S.: Endothelhyperplasie als Systemerkrankung des hämatopoetischen Apparats, Deutsches Arch. f. klin. Med. **138**:291, 1921.

42. Sachs, F., and Wohlwill, F.: Systemerkrankungen des retikuloendothelialen Apparats und Lymphogranulomatose, Virchows Arch. f. path. Anat. **264**:640, 1927.

43. Epstein, E.: Die generalisierten Affektionen des histiozytären Zellsystems (Histiocytomatosen), Med. Klin. **21**:1501 (Oct. 2) 1925.

44. Weidenreich, F.: Die Leucozyten und verwandte Zellformen, Wiesbaden, J. F. Bergmann, 1911.

45. Patella, V.: La genesi endoteliale dei monociti, dell forme di passagie e dei cosiddetti linfociti del sangue, Hematologica **4**:59, 1923.

46. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

cally and culturally, and which now were seen to be functionally active in the storage or phagocytosis of dyes. These cells, functionally similar, were thus elevated to a "system" by Aschoff and his co-workers, and since they occurred in the reticulum of various organs (reticular cells) and lined sinusoids in the same organs (endothelial cells) the system was called "reticulo-endothelial."

During the course of the last fifteen years, other methods of study have demonstrated the functional identity of the cells of this system. It was found that the histiocytes had the power of fat storage, and in the marked lipoidemia which often accompanies diabetes mellitus, these cells were found to be filled with fat (Schöndorff,³¹ Schultze³²). Gaucher's disease was found to be an abnormal storage in the reticulo-endothelial system of a peculiar lipoidal material, probably kerosin.³³ The system has a great capacity for the storage of cholesterol and lipid-protein mixtures (Chalatow³⁴) and for casein (Kuczynski³⁵). Niemann's disease represents probably a pathologic storage of cholesterol (Niemann,³⁶ Bloom³⁷). Xanthomatosis is shown by Rowland³⁸ to be due to infiltration of the reticulo-endothelial system with lipid substances. Hodgkin's disease is considered by several authors, including Pincy,³⁹ to be a reticulo-endotheliosis. Indeed the conception of reticulo-endotheliosis, an overgrowth of the reticulo-endothelial system, has gained a great deal of favor in recent years.

Using this classification, monocytic leukemia is to be regarded as leukemic reticulo-endotheliosis; there is also aleukemic reticulo-endo-

31. Schöndorff, W.: Ueber die lipoidzellige Hyperplasie der Milz bei diabetischer Lipoidämie, *Virchows Arch. f. path. Anat.* **258**:246, 1925.

32. Schultze, W. H.: Ueber grosszellige Hyperplasie der Milz bei Lipoidämie (Lipoidzellen-hyperplasie), *Verhandl. d. deutsch. path. Gesellsch.* **15**:47, 1912.

33. Epstein, E.: Beitrag zur Pathologie der Gaucherischen Krankheit, *Virchows Arch. f. path. Anat.* **253**:157, 1924.

34. Chalutow, S. S.: Die anisotrope Verfettung in Lichte der Pathologie des Stoffwechsels, Jena, Gustav Fischer, 1922.

35. Kuczynski, M. H.: Edwin Goldmanns Untersuchungen über celluläre Vorgänge im Gefolge des Verdauungsprozesses auf Grund ungeschlossener Präparate und durch neue Versuche ergänzt, *Virchows Arch. f. path. Anat.* **230**:185, 1922.

36. Niemann, A.: Ein unbekanntes Krankheitsbild, *Jahrb. f. Kinderh.* **70**:1, 1914.

37. Bloom, W.: Splenomegaly (Type Gaucher) and Lipoidhistiocytosis (Type Niemann), *Am. J. Path.* **1**:595, 1925.

38. Rowland, R. S.: Xanthomatosis and the Reticulo-Endothelial System, *Arch. Int. Med.* **42**:611 (Nov.) 1928.

39. Pincy, A.: Recent Advances in Hematology, Philadelphia, P. Blakiston's Son & Company, 1927, p. 47.

transitions between monocytes and lymphocytes, and monocytes and lymphocytes can always be separated easily. The unitarians, however, say that transitions between lymphocytes and monocytes can be seen, and some of them maintain that lymphocytes cannot be distinguished clearly from monocytes (Downey,⁴⁹ Weidenreich,⁴⁴ Patella,⁴⁵ Bloom²²).

The dualistic school—Naegeli—has no supporters. Ehrlich²¹ thought the monocytes to be transitions between the granular cells and the lymphoid cells, but this view has long since been discarded.

The consensus at the present time is that the monocyte is derived directly from the histiocytes which form the reticulo-endothelial system. This opinion is based on: (1) morphologic characteristics: transitions between histiocytes and monocytes are clearly seen both under normal and under pathologic conditions (as in leukemias, malaria, etc.); (2) cultural characteristics: tissue cultures by Maximow, cell cultures by Maximow and others; (3) bacteriologic investigations: production of monocytosis by injection of *B. monocytogenes* (Murray,⁵⁰ Lang⁵¹); examination of the animals after death; studies by this method combined with vital staining; (4) vital staining methods: intravital staining in the animal; supravital staining.

CONCEPTIONS OF MONOCYTIC LEUKEMIA

The medical world has been disinclined to accept this third form of leukemia, the monocytic. This has been due in part, of course, to the fact that there is as yet no unified conception concerning the nature or the derivation of the monocyte. In most part, acceptance has probably been delayed because the conception of only two types of leukemia—myelogenous and lymphatic—has become so firmly ingrained that a third seems unbelievable. Again, overgrowth of the histiocytic tissue (reticulo-endothelial system) in the bone-marrow must necessarily bring with it more or less overgrowth of the closely adjacent myeloid tissue, so that if a monocytic leukemia lasts long enough, it becomes a mixed leukemia.

What are the expressions of the various writers on the subject of monocytic leukemia? In 1925, Hirschfeld⁵² wrote (on the basis of the first three reported cases): "Because of the few cases of monocytic leukemia, the relationship to the other types of leukemia is obscure.

49. Downey, H.: The Occurrence and Significance of the "Myeloblast" Under Normal and Pathological Conditions, *Arch. Int. Med.* **33**:301 (March) 1924.

50. Murray, E. G. D.; Webb, R. A., and Swann, M. B. R.: Disease of Rabbits Characterized by Large Mononuclear Leucocytosis, Caused by Hitherto Undescribed Bacillus, *Bacterium Monocytogenes*, *J. Path. & Bact.* **29**:407 (Oct.) 1926.

51. Lang, F. J.: Zur Monozytenfrage, *Folia haemat.* **36**:383, 1928.

52. Hirschfeld, H.: Leukemia, in *Handbuch der Krankheiten des Blutes und der blutbildenden Organe*, Berlin, Julius Springer, 1925, vol. 1, p. 411.

must occupy an autonomous position. The histologic character of the monocyte closely resembles that of the histiocyte. Culturally, they are both actively phagocytic. After intravenous injections of vital dye, certain fixed histiocytes become hypertrophied and desquamate, and are seen in the peripheral blood. According to Maximow, histiocytes never get into the circulating blood, but monocytes are formed directly from them by proliferation in the spleen, liver, bone-marrow and lymph nodes. Monocytes may thus be considered a connecting link between the blood and the lining tissue.

This monophyletic or unitarian conception differs but little from the polyphyletic, the chief exponents of which are Schilling⁴⁷ in Germany,

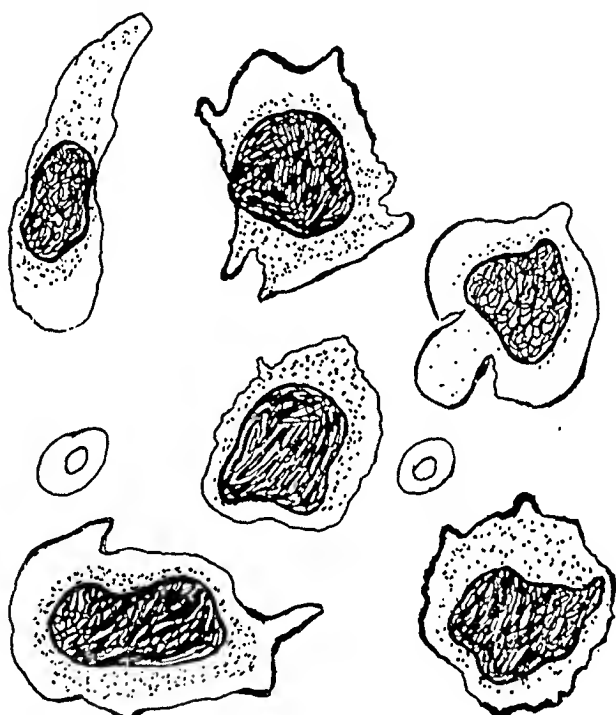


Fig. 4.—Sketches of representative histiocytes ($\times 1,500$) seen on Dec. 4, 1928. The large size, the polymorphism, the irregular cytoplasmic borders representing a very active cell, the spongy nucleus and the characteristic perinuclear arrangement of the granules are shown.

Ferrata⁴ in Italy, Merklen and Wolf⁴⁸ in France and Kiyono³⁰ in Japan. The monophyletic school says that all the blood cells are derived from a primitive blood cell, to which all are agreed. The polyphyletic or trinitarian school says that there is differentiation in the embryo into three types of blood-forming tissue—myeloid, lymphatic and reticulo-endothelial (which most of the unitarians readily admit)—but that this differentiation is irreversible. In other words, there can be no

47. Schilling, V.: *Das Blutbild und seine klinische Verwertung*, ed. 2, Jena, Gustav Fischer, 1922.

48. Merklen, M., and Wolf, M.: *Le monocyte*, *Ann. d'anat. path.* 4:621, 1927.

The appearance of myeloid elements in the blood in Fleischmann's and Hirschfeld's case as well as the marked degree of myeloid degeneration in Fleischmann's case make one think that this is an ordinary myelogenous leukemia with a one-sided differentiation into monocytes."

Naegeli,⁴⁶ writing in the last edition (1923) of his textbook, considered (also on the basis of the first three cases and of three questionable cases he had seen) that "so-called monocytic leukemia was a temporary variant of myelogenous leukemia into which it passes unless death intervenes."

Piney,³⁹ writing in 1927, said that the "evidence seems to be all in favor of the conception of monocytic leukemia belonging to the group of myelosis, and not being a special form of leucosis (leukemia) depending upon proliferation of the cells of a third hematopoietic system."

Schilling-Torgau,¹ in the original article and in his textbook, said that there is no doubt but that there is a third type of leukemia just as there are three types of white blood cells. Ferrata and Reitano,¹⁷ in discussing the appearance of histiocytes in leukemia and in other conditions, brought out the fact of the presence of large numbers of histiocytes in monocytic leukemia, which they recognized as an entity. Ferrata and Reitano¹⁷ expressed the belief that there is an acute histiocythemic syndrome.

Krahn,¹² in a critical analysis of "reticulo-endotheliosis" in which he discussed a few of the reported cases of monocytic leukemia, came to the conclusion that reticulo-endotheliosis is merely a reaction to infection. He said that the whole question of the monocyte is so uncertain that the conception of monocytic leukemia as a third entity is not to be considered. This analysis appears deficient in that only a few cases are mentioned, and these are doubtful. Consideration of acute monocytic leukemia as an infection may perhaps be correct, but the other acute leukemias appear to be just as infectious, so that it would be advisable, if Krahn were to be followed, to drop the entire conception of acute leukemia.

Fleischmann,⁵³ in 1915, thought that his case was at first monocytic, later becoming mixed monocytic-myelogenous. Bingel,⁵⁴ in 1916, observed that if these cases were seen more frequently, the existence of a third form of leukemia would thereby be proved. Rosenthal,¹⁵ in 1921, strongly favored the third form of leukemia based on the third type of white blood cell, the monocyte. Ewald, Frehse and Hennig,⁵⁵

53. Fleischmann, P.: Der zweite Fall von Monozytenleukämie, *Folia haemat.* **20**:19 (Oct. 1) 1915.

54. Bingel: Monozytenleukämie? *Deutsche med. Wchnschr.* **42**:1503 (Dec. 7) 1916.

55. Ewald, Frehse and Hennig: Akute Monozyten- und Stammzellen Leukämien, *Deutsches Arch. f. klin. Med.* **138**:353 (Feb.) 1922.

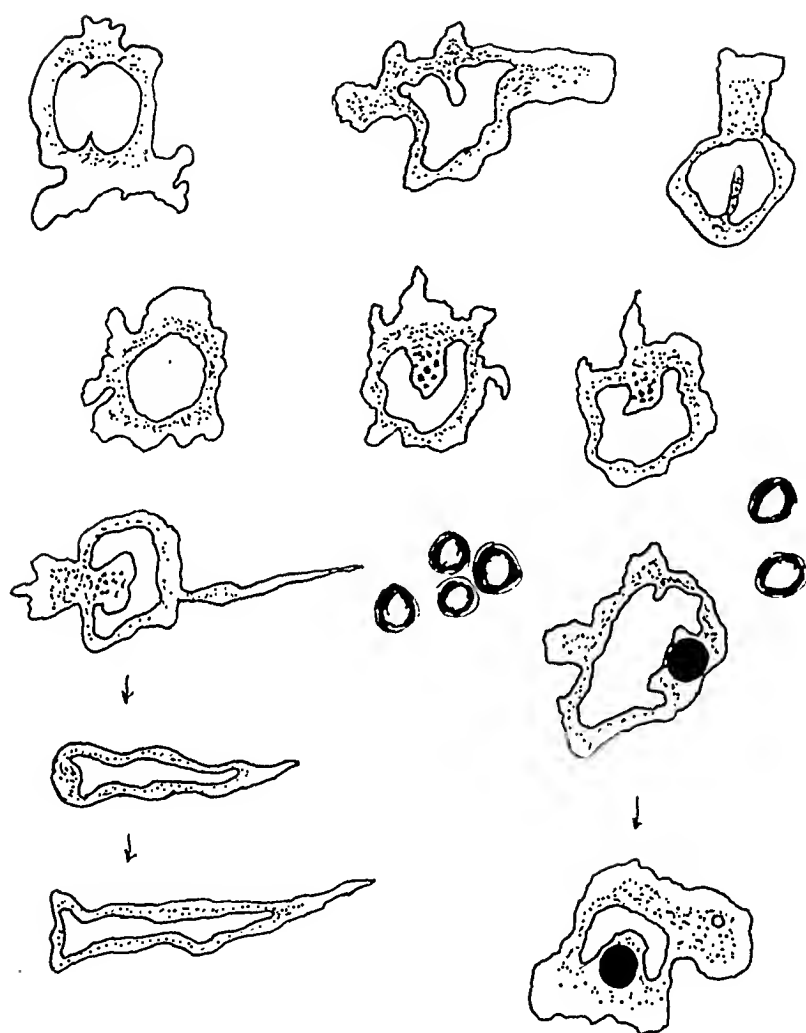


Fig. 5.—Drawings made from living white blood cells on Nov. 27, 1928. Neutral red, 20 drops (of stock solution) and Janus green, 5 drops (of stock solution) in 2 cc. of absolute alcohol was used as stain; the preparation was kept at 37.5 C. in a hot box. Histiocytes and monocytes are to be seen, the dividing line between the two being difficult to make. Those cells with marked indentation of the nucleus and clustering of neutral red granules in the bend of the nucleus are probably monocytes. The rapid changes in size and shape of these cells are shown in the lower drawings. These changes took place within from two to three minutes. The histiocyte on the right has a red blood cell inclusion and changed its size very rapidly, apparently in attempts to digest the red cell. A small vacuole appeared in this histiocyte after two minutes. Several red blood cells are pictured for comparison in size. Note the tendency of the neutral red granules to remain near the nucleus, their entrance into the pseudopods being delayed a varying length of time. The mitochondria, which take the Janus green, are seen as delicate filaments interspersed among the granules. Oil immersion, Leitz, 1/12 objective, no. 10 eyepiece; $\times 1,000$.

Supravital staining of the blood served to confirm the diagnosis of the type cell, the histiocyte.

A review of the literature on the subject is presented. Since the conception of the third form of leukemia is linked intimately with the studies on the reticulo-endothelial system and on the monocyte, these subjects are discussed in some detail.

The monocyte appears to be a distinctive cell directly derived from the reticulo-endothelial system. Various disorders of this system have been described: abnormal storage (Gaucher's disease, Niemann-Pick's disease, xanthomatosis); irritations due to infections (monocytosis); tumor growth (endothelioma, reticuloma), and proliferation (leukemia). The proliferative lesions—reticulo-endotheliosis—may be leukemic or aleukemic. Leukemic proliferation results in the clinical entity known as monocytic leukemia.

It is thought, therefore, that the third type of leukemia should be added to the two accepted types. Though apparently much rarer than either myelogenous or lymphatic leukemia, clearcut cases of monocytic leukemia at times appear and should not escape recognition.

in 1922, in discussing "Stammzellenleukämie," concluded that a specific irritant may bring about marked cytogenesis of the mother cells of the hematopoietic tissue and thus produce a leukemia in which are present "Stammzellen," the forerunners of the monocytes. Ewald,⁵⁶ in 1923, thought that acute reticulo-endotheliosis was a third type of leukemia in which the primordial or "Stammzellen" were involved.

Komiya and Hayishi,⁵⁷ in 1921, thought definitely that there was a third type of leukemia, as did Hoff⁵⁸ in 1926. On the other hand, Alder,¹⁰ in 1923, thought that "the expression monocytic leukemia is often incorrectly used and without foundation. True monocytic leukemia, as the observation of Reschad and Schilling is extremely rare." He said, too, that "it is advisable to let the idea of monocytic leukemia go or turn to it with reserve. . . ." All the authors who described cases in 1928 are definite as to the third type of leukemia, which most of them called reticulo-endotheliosis (Ugriumov,¹³ Schwirtschewskaja,¹⁶ Hittmair⁵⁹). The latter two authors discussed the various types of reticulo-endotheliosis—leukemic, aleukemic, etc. Merklen and Wolf,² whose work on monocytic leukemia has been exhaustive, distinguished the three types of leukemia.

It is probably true that the more "acute" a case of leukemia is, the more primitive does the predominating cell type become. Since the most primitive cell is the hemocytoblast (hemohistioblast, histiocyte, "Stammzell"), these cells should appear in the most acute cases of leukemia. Since these cells may potentially produce all the other white blood cells, it may well be that certain cases of acute leukemia merge one into the other. Thus, monocytic leukemia may be related more or less closely to myelogenous leukemia. It is felt, however, that certain cases of monocytic leukemia are "pure," with intense proliferation of the histiocytic system and but little or no involvement of the other systems or tendency to develop into the other forms of leukemia.

SUMMARY AND CONCLUSIONS

Two cases are presented in which the diagnosis of acute monocytic leukemia was made. With these cases, there have been eighteen well substantiated instances of the disease since the first report in 1913.

56. Ewald, O.: Die leukämische Retikuloendotheliose, *Deutsches Arch. f. klin. Med.* **142**:222, 1923.

57. Komiya, E., and Hayishi, T.: Ueber die Monozyten- und Monozytenleukämie Frage beurteilt von einem jüngst von uns beobachteten Fall, *Mitt. a. d. Med. Fakult. d. k. Univ. zu Tokyo* **27**:375 (Nov.) 1921.

58. Hoff, F.: Beiträge zur Pathologie der Blutkrankheiten, *Virchows Arch. f. path. Anat.* **261**:142, 1926.

59. Hittmair, A.: Zur Frage der sogenannten Retikuloendotheliosen, *Folia haemat.* **37**:321 (Dec.) 1928.

writer. No cases among the Chinese have been reported in the medical literature. It is likewise rare among the Japanese according to information obtained in conversation with Japanese physicians. Unfortunately, the Japanese death statistics do not list pernicious anemia as a separate cause of death.

In table 1 is given the death rate from pernicious anemia in the states of the registration area of the United States. The data leave no doubt that there is a low death rate in the southern states, the mean for eleven states being 2.1 per hundred thousand of population. Next comes the mountain and plateau states with 4, and finally the central

TABLE 1.—Deaths from Pernicious Anemia per 100,000 Estimated Population in the States of the Registration Area
(Mean for the years 1921 to 1926)

Southern States		Central and Northern States	
Florida	3.8	Maine	7.7
South Carolina.....	1.2	Vermont	9.2
Georgia	1.4	New Hampshire.....	9.4
Alabama	1.2	Massachusetts	7.4
Mississippi	1.0	Connecticut	5.3
Louisiana	1.7	Rhode Island.....	6.0
North Carolina.....	1.7	New York.....	5.5
Virginia	2.2	Michigan	9.7
Tennessee	2.8	Wisconsin	9.0
Kentucky	2.8	Minnesota	9.7
West Virginia.....	3.5	North Dakota.....	5.6
Mean for 11 states.....	2.1	Washington	6.3
Western Plateau States		Oregon	6.7
Arizona	2.7	California	7.4
Utah	5.0	Kansas	6.9
Colorado	6.0	Nebraska	6.9
Wyoming	2.8	Iowa	10.4
Idaho	3.0	Missouri	4.7
Montana	4.3	Illinois	6.2
Mean for 6 states.....	4.0	Indiana	6.4
		Ohio	6.0
		Pennsylvania	4.7
		New Jersey.....	4.4
		Maryland	3.7
		Delaware	3.8
		Mean for 25 states.....	6.8

and northern states with rates ranging up to 10.4, the mean being 6.8 per hundred thousand of population. The low incidence among Negroes would account for a part of the low death rate of the southern states, but if the total deaths from pernicious anemia were calculated only on the white population, the rate would still be less than half that found in the northern states. It is to be noted that the states of the upper Mississippi and Missouri river valleys and of northern New England, where the stimulating extremes of climate are most often encountered, are the places of highest incidence. Florida and Colorado show high rates for their locations, probably because of migration of the more well-to-do people from states with higher rates.

Table 2 sets forth similar data for other countries. In this table an arbitrary division is made, one group containing all countries with a

GEOGRAPHIC OR CLIMATIC VARIATIONS IN THE DEATH RATE FROM PERNICIOUS ANEMIA, EXOPHTHALMIC GOITER, ADDISON'S DISEASE AND ANGINA PECTORIS *

C. A. MILLS, M.D.

CINCINNATI

In a preceding paper¹ it was indicated that the death rate from diabetes is apparently influenced to a marked degree by climatic conditions. The rate diminishes as one nears the equator and in general increases in the opposite directions. This was clearly shown for the states of the United States, for the countries of Europe and for Australia and New Zealand. It was suggested that this increase in the cooler, more stimulating regions probably results from an exhaustion effect of overstimulation by the highly changeable climate. To rule out the consumption of sugar as a responsible factor, the rate of the consumption of sugar was found for many countries and compared with the death rate from diabetes.² There was not found sufficient correlation between the two to indicate a cause and effect relationship.

It has often been suggested that overeating of other than sugar foods may be responsible for the increase in deaths from diabetes. Calculation of the consumption of food in general, however, becomes too involved to be practicable. Efforts have been directed along other lines, therefore, in an attempt to find the reason for such an alarming increase in diabetes. Other diseases of an exhaustive or overstimulative type have been studied to determine whether they exhibit similar geographic variations.

PERNICIOUS ANEMIA

Very little has been written on the geographic distribution of pernicious anemia. Bunting³ said that there was a wide distribution, with few local variations, and that, although most reports had been of cases in the white race, the disease occurred in other races also. During a two years' stay in China, not a single case was seen or heard of by the

* Submitted for publication, April 28, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

1. Mills, C. A.: Diabetes Mellitus: Is Climate a Responsible Factor in the Etiology? **46:569** (Oct.) 1930.

2. Mills, C. A.: Sugar Consumption in the Etiology of Diabetes Mellitus, **46:582** (Oct.) 1930.

3. Bunting, C. H.: Bull. Johns Hopkins Hosp. **16:222**, 1925.

EXOPHTHALMIC GOITER

Since this disease probably most nearly represents the effects of individual metabolic overstimulation, it was deemed advisable to include it in the statistical study. There has been much speculation as to the basis of this overstimulation, but no definite proof has been advanced. Climate has not been considered as an important etiologic factor.

In table 3 is presented the death rate by states in the United States for the year 1927. Not only is there an exceedingly low death rate from this cause in the southern states (1.5) as compared with the north (4), but among the southern states it is seen that the rate rises with the pro-

TABLE 3.—Deaths from Exophthalmic Goiter per 100,000 Estimated Population in the States of the Registration Area for 1927

Southern States		Central and Northern States	
Florida	1.3	Maine	1.4
South Carolina.....	0.8	Vermont	4.0
Georgia (1928).....	0.9	New Hampshire.....	1.1
Alabama	1.1	Massachusetts	1.3
Mississippi	0.8	Connecticut	1.5
Louisiana	1.2	Rhode Island.....	1.9
Arkansas	0.7	New York.....	2.7
North Carolina.....	1.1	Michigan	7.5
Arizona	1.5	Wisconsin	8.0
Tennessee	1.6	Minnesota	5.7
Kentucky	2.3	North Dakota.....	3.1
Virginia	2.7	Washington	5.8
West Virginia.....	3.5	Oregon	7.1
Mean for 13 states.....	1.5	California	2.8
Western Plateau States		Kansas	5.3
Utah	4.2	Nebraska	4.4
Colorado	4.7	Iowa	4.5
Wyoming	1.3	Missouri	5.0
Idaho	4.0	Illinois	7.1
Montana	3.4	Indiana	7.8
Mean for 5 states.....	3.5	Ohio	7.0
		Pennsylvania	3.8
		New Jersey.....	1.8
		Maryland	3.4
		Delaware	1.6
		Mean for 25 states.....	4.02

gression from south to north. Florida provides the exception here as in the case of pernicious anemia and diabetes mellitus, and probably for similar reasons; i. e., there is a migration on a large scale from northern states where the rates are higher.

It is interesting to note the low rate in all states having comparatively extensive contact with the Atlantic ocean, even up to, and including, Maine, while the Pacific coast states show high rates. No explanation can be offered for this observation at present. One might be tempted to attribute the low rate in the coastal states of the south to the same cause, but in this region the inland states also show comparatively low rates. The north central states that have such a high prevalence of simple goiter also have the highest death rates from exophthalmic goiter.

rate greater than 3 per hundred thousand of population and the other group, countries below this level. A comparison of this table with a similar table for the death rate from diabetes shows a striking likeness. The same countries that have such a high, and increasing, death rate from diabetes are also the ones similarly afflicted with pernicious anemia, while near the equator both disease are much less fatal. This difference cannot be racial, for in the countries with low rates there are Italy, Uruguay and Iceland mainly populated by the white race, Ceylon by Indians, the Philippines and the Straits Settlements by the yellow and brown races and Nigeria and Haiti by the black.

TABLE 2.—*Pernicious Anemia Death Rates in Various Countries*

Country	Year	Deaths per One Hundred Thousand Population from Pernicious Anemia	Deaths from Pernicious Anemia as Percentage of Total Deaths
Northern Ireland.....	1927	10.7	0.73
Scotland	1926	10.6	0.80
Canada	1926	9.3	0.81
Irish Free State.....	1927	7.4	0.50
England and Wales.....	1927	6.8	0.55
United States.....	1926	5.7	0.46
Norway	1926	5.4	0.50
Netherlands	1927	4.4	0.43
New Zealand.....	1928	3.8	0.45
South Africa.....	1926	3.1	0.32
Italy	1925	2.3	0.14
Uruguay	1927	2.2	0.19
Barbados	1927	2.0	0.10
Nigeria	1927	2.0	0.10
Philippine Islands.....	1925	1.8	0.10
Straits Settlement.....	1927	1.5	0.05
Hawaii	1927-8	1.5	0.13
Iceland	1911-15	1.2	0.09
Haiti	1927	0.3	0.06
Ceylon	1928	0.3	0.01

There would, therefore seem to be a definite geographic, or climatic, distribution of deaths from this cause. Iceland forms one exception here, as it did for diabetes. Although Japan and northern China should fall, geographically, into the upper half of table 2 in regard to their distance from the equator, their actual death rate from pernicious anemia must be fully as low as in the tropical countries. Whether this is due to racial influence or to the severe tropical summer which they must endure, can only be conjectured.

In the countries with high death rates from pernicious anemia, the rates were rising rapidly up to 1926, but in almost all these same countries there has been a marked fall since that year. This probably results from the relief afforded by liver diets and liver extracts during this recent period.

Straits Settlements in the first group and of Norway in the second group, the same distribution of the death rates was found as that for diabetes and pernicious anemia. The countries farther from the equator have the higher rates, while the warmer countries have the lower rates. Japan, although placed well northward, falls into the tropical group. Personal observation in North China indicated a similar low incidence of exophthalmic goiter there. It is probably more than a coincidence that the orient should be so similar to the tropics in the low death rates for these diseases.

TABLE 5.—Deaths from Addison's Disease and Tuberculosis (All Forms) per 100,000 Population in the States of the Registration Area

	Tuberculosis (All Forms)			Tuberculosis (All Forms)	
	Addison's Disease 1927	Mean for 1920, 1925, 1926		Addison's Disease 1927	Mean for 1920, 1925, 1926
Southern States			Central and Northern States		
Florida	0.07	91.7	Maine	0.3	79.3
South Carolina	0.06	101.6	Vermont	0.0	77.7
Georgia	0.05	New Hampshire	0.7	77.7
Alabama	0.1	97.1	Massachusetts	0.3	90.1
Mississippi	0.06	115.0	Connecticut	0.3	89.8
Louisiana	0.06	119.1	Rhode Island	2.9	95.4
Arkansas	0.2	New York	0.4	100.9
North Carolina	0.1	104.6	Michigan	0.4	73.2
Arizona	0.2	328.5	Wisconsin	0.4	70.8
Tennessee	0.2	150.0	Minnesota	0.6	70.9
Kentucky	0.2	131.6	North Dakota	0.9	47.8
Virginia	0.1	119.1	Washington	0.3	83.6
West Virginia	0.1	76.7	Oregon	0.3	71.9
Mean for 13 states..	0.1		California	0.5	145.5
Western Plateau States			Kansas	0.2	44.5
Utah	1.0	34.1	Nebraska	0.4	35.9
Colorado	0.6	174.0	Iowa	0.4	40.0
Wyoming	0.0	28.6	Missouri	0.5	92.7
Idaho	0.2	34.2	Illinois	0.3	85.0
Montana	0.6	62.7	Indiana	0.4	91.4
Mean for 5 states...	0.5		Ohio	0.5	83.7
			Pennsylvania	0.3	86.3
			New Jersey	0.3	92.7
			Maryland	0.2	127.1
			Delaware	0.4	118.5
			Mean for 25 states...	0.5	

Jamaica and the Straits Settlements, the two tropical regions that have the higher exophthalmic goiter rates, have both developed this high rate within the last three or four years. Previous to that time there were no deaths from these diseases in most years, with a very low average rate. It would indeed be of great interest to find what economic or health changes have taken place recently in these localities.

ADDISON'S DISEASE

Tuberculosis of the suprarenal glands is the most frequent pathologic observation following death from Addison's disease, and yet if mortality statistics for this disease are at all reliable, its incidence does not correspond even remotely to the incidence of tuberculosis. The death rates, by states, for these two diseases are shown in table 5. Table

It is of interest in this connection to compare the death rates from this cause in the provinces of Canada:

<i>Deaths from Exophthalmic Goiter per 100,000 Population, 1926</i>	<i>Deaths from Exophthalmic Goiter per 100,000 Population, 1926</i>
Canada 3.5	Ontario 6.3
Prince Edward Island..... 0.0	Manitoba 3.6
Nova Scotia 0.9	Saskatchewan 2.4
New Brunswick 1.0	Alberta 2.1
Quebec 1.6	British Columbia..... 4.4

Here again is seen a very low rate in the Atlantic coast provinces, a very high rate in the region of the Great Lakes, a medium rate in the

TABLE 4.—*Death Rates from Exophthalmic Goiter in Various Countries*

Country	Year	Deaths from Exophthalmic Goiter Per One Hundred Thousand Population
Jamaica	1927	4.2
United States.....	1927	4.0
New Zealand.....	1928	3.7
Canada	1926	3.5
England and Wales.....	1928	2.7
North Ireland.....	1928	2.4
Straits Settlements.....	1927	2.0
Scotland	1928	1.9
Irish Free State.....	1927	1.7
South Africa.....	1926	1.3
Holland	1928	1.1
Switzerland	1925	1.0
Japan	1918	0.56
Norway	1926	0.4
Italy	1925	0.4
Uruguay	1927	0.35
Hawaii	1927-8	0.3
Philippine Islands.....	1925	0.17
Spain	1926	0.17
Haiti	1927	0.05
Ceylon	1928	0.04
Colombia	1927	0.04
Grenada	1927	0.00
British Guiana.....	1927	0.00
Barbados	1927	0.00

prairie provinces and a high rate again along the Pacific coast. This very low rate along the Atlantic coast in the United States and Canada and the high rate along the Pacific coast deserve further study. McClendon⁴ has attempted to correlate the incidence of exophthalmic goiter with low iodine values in surface and drinking waters, but his data are not entirely convincing. It is hoped that this question may be taken up in a future article.

In table 4 the death rate from exophthalmic goiter is given by countries, arranged in a descending order of death rate values. An arbitrary division is made, with those countries having a rate of 1 or more per hundred thousand of population in one group and those with a rate below 1 in the second group. With the exception of Jamaica and the

4. McClendon, J. F.: Inverse Relation Between Iodin in Food and Drink and Goiter, Simple and Exophthalmic, J. A. M. A. 82:1668 (May 24) 1924.

ANGINA PECTORIS

During almost two years of hospital experience in China the author saw little advanced arteriosclerosis or its complications in the Chinese people. Blood pressure in the Chinese ranges considerably below the levels common in northern United States, and the basal metabolism and general scale of physical activity are correspondingly low. Since a high metabolic drive may perhaps be the causative force in a great portion of the cases of arteriosclerosis seen today, it was deemed advisable to get mortality statistics on this point if possible. Angina pectoris was considered as probably the best index to vascular change that would

TABLE 7.—Deaths from Angina Pectoris per 100,000 Population in the States of the Registration Area for 1927

Southern States		Central and Northern States	
Florida	16.0	Maine	39.6
South Carolina.....	11.7	Vermont	33.4
Georgia	9.4	New Hampshire.....	47.0
Alabama	6.7	Massachusetts	22.4
Mississippi	7.1	Connecticut	18.0
Louisiana	12.8	Rhode Island.....	17.9
Arkansas	4.7	New York.....	19.6
North Carolina.....	9.5	Michigan	14.1
Arizona	9.4	Wisconsin	11.7
Tennessee	9.7	Minnesota	10.8
Kentucky	10.0	North Dakota.....	9.0
Virginia	13.6	Washington	17.4
West Virginia.....	7.5	Oregon	18.2
Mean for 13 states.....	9.2	California	23.7
Western Plateau States		Kansas	13.1
Utah	10.2	Nebraska	12.7
Colorado	15.6	Iowa	16.7
Wyoming	6.6	Missouri	11.0
Idaho	9.4	Illinois	12.3
Montana	8.8	Indiana	18.8
Mean for 5 states.....	10.1	Ohio	14.7
		Pennsylvania	12.5
		New Jersey.....	16.7
		Maryland	19.2
		Delaware	15.2
		Mean for 25 states.....	18.6

appear in mortality statistics. The certainty of diagnosis in this disease should not differ greatly in different countries, so that valuable comparison should be obtained.

In table 7 is shown the death rate from angina pectoris in the various states for 1927. The rate in the southern group of states is seen to be just about half that of the northern states. The rate in Negroes is lower than that in the white population in the south, but the rate in the white population in the south is only about two-thirds as high as that in the north (see table for white and Negro rates). Table 8 gives a similar comparison by countries. Here the same climatic differences in the death rate are noted as those found for the diseases previously considered. This is the more interesting in that this disease can scarcely be considered in any way as a direct metabolic disturbance; and still it shows the same world variations in death rate as were manifest for diabetes, exophthalmic goiter, etc.

10 gives a comparison of the various rates for white and colored population in the states that classify their deaths in this way. In this table it is seen that although the death rate from tuberculosis in the colored population is about three times as high as that in the white, Addison's disease is rare. It seems unlikely, therefore, that the clinical diagnosis of Addison's disease, on which most death certificates are based, bears any direct relationship to the incidence of tuberculosis among the population. A similar comparison of data based on diagnoses at autopsy would be more valuable. An effort will be made to get such a comparison.

TABLE 6.—*Death Rate from Addison's Disease in Various Countries*

Country	Year	Deaths per One Hundred Thousand Population per Year
Jamaica	1927-8	0.7
New Zealand.....	1921-3	0.6
England and Wales.....	1915-28	0.6
Scotland	1923-8	0.6
Canada	1921-6	0.5
Australia	1921-7	0.5
North Ireland.....	1927-8	0.5
Irish Free State.....	1927-8	0.5
Switzerland	1911-20	0.5
Argentina	1913	0.2
Prov. of Tucuman.....	1924	0.5
Prov. of Buenos Aires.....	1924	0.4
Norway	1922-6	0.4
United States.....	1922	0.3
Union of South Africa.....	1922-6	0.3
Netherlands	1922-8	0.3
Hawaii	1927-8	0.3
Iceland	1911-15	0.2
Costa Rica.....	1927	0.2
Uruguay	1927	0.18
Cuba	1921-5	0.09
Ceylon	1928	0.04
Japan	1918	0.04
Philippine Islands.....	1925	0.01
Barbados	1927-8	0.00
Straits Settlements.....	1924-8	0.00
Granada	1923-8	0.00
Nigeria	1926-7	0.00

The very low mean rate, 0.1 per hundred thousand of population, from Addison's disease in the southern states, and the mean rate of 0.5 in the northern states is difficult to explain except on a climatic basis. The more intense industrialization in the north cannot be blamed, for the highest rates are found in the states with predominantly rural population. Neither can the rarity of the disease in the Negro be the reason for the low southern rate, for table 10 shows the rate for the southern white population to be far below that of the north. It would seem, then, most likely that the greater climatic stimulation of the northern states is responsible for the deaths from suprarenal failure. Table 6, presenting the death rates from Addison's disease over the world, shows the same climatic variations as were noted for the other metabolic diseases and for this disease in the United States.

basic factors in determining the prevalence of the diseases considered. In the case of Addison's disease the lack of association with tuberculosis is strikingly brought out. The Negroes have practically no deaths from Addison's disease, although the death rate from tuberculosis is roughly three times as high as that of the white population, and shows

TABLE 9.—Deaths from Certain Acute Infectious Diseases per 100,000 Estimated Population in the States of the Registration Area

	Pneumonia (All Forms) 1926	Acute and Chronic Nephritis 1926	Acute Rheu- matic Fever 1927
Mean for 11 southern states.....	80.1	84.0	1.8
Mean for 5 western plateau states.....	74.1	53.8	2.9
Mean for 25 central and northern states..	98.3	97.5	2.3

TABLE 10.—Deaths from the Various Diseases Considered, per 100,000 Estimated "White" and "Colored" Population (1927)

State	Pernicious Anemia		Exophthalmic Goiter		Addison's Disease		Angina Pectoris	
	White	Colored	White	Colored	White	Colored	White	Colored
Florida	3.0	2.3	1.6	0.5	0.1	0.0	19.3	8.6
Alabama	1.8	0.8	1.0	1.3	0.12	0.11	8.8	2.8
Mississippi	0.9	0.5	1.1	0.6	0.1	0.0	11.6	3.0
Georgia (1928).....	1.1	1.2	1.2	0.4	0.1	0.0	11.5	6.0
Louisiana	1.7	0.15	1.1	1.5	0.08	0.0	13.4	12.0
Arkansas	1.0	1.4	0.6	0.8	0.3	0.0	5.9	2.4
South Carolina.....	1.9	1.1	1.2	0.3	0.1	0.0	15.4	7.7
North Carolina.....	2.4	1.2	1.3	0.7	0.15	0.0	11.0	5.7
Tennessee	2.7	1.2	1.5	2.1	0.2	0.0	11.0	8.7
Virginia	2.5	1.5	2.7	2.5	0.2	0.0	14.7	10.8
Kentucky	3.2	1.4	2.1	4.7	0.13	0.5	9.2	19.4
Maryland	2.0	0.4	3.7	2.0	0.2	0.0	21.3	8.2
Missouri	4.4	0.0	4.7	2.5	0.24	0.0	19.9	9.1

State	Acute Rheu- matic Fever		Tuberculosis (All Forms) 1926		Acute and Chronic Nephritis 1926		Pneumonia (All Forms) 1926	
	White	Colored	White	Colored	White	Colored	White	Colored
Florida	2.0	3.0	57.9	162.6	119.4	146.3	68.9	125.2
Alabama	1.7	2.6	52.6	170.1	72.8	109.1	77.6	129.8
Mississippi	0.9	2.2	50.7	163.1	96.7	124.4	79.2	105.9
Georgia (1928).....
Louisiana	1.0	3.0	59.7	185.5	91.0	146.0	74.2	140.8
Arkansas	1.1	2.5
South Carolina.....	2.1	3.0	42.5	142.1	101.6	138.0	72.4	104.5
North Carolina.....	2.4	3.2	64.1	179.4	88.8	129.8	78.0	131.6
Tennessee	2.0	4.0	111.0	320.7	67.1	138.5	89.7	183.9
Virginia	2.1	4.9	71.5	191.9	97.3	149.8	68.6	133.6
Kentucky	2.7	12.8	106.2	299.7	78.7	212.7	85.8	200.6
Maryland	2.3	11.7	86.3	257.6	143.5	227.1	121.4	284.3
Missouri	1.3	5.1

a great increase toward the north. This increase in rate toward the north is shown for both the white and colored population of the south for most of the metabolic diseases.

COMMENT

No doubt various objections will be raised against interpretations based on the death statistics presented here. Foremost among these objections will be the argument that the low rates for these metabolic

ACUTE INFECTIOUS DISEASES

In considering the data presented for the metabolic diseases and angina pectoris, many will say that the differences in death rates from these diseases may be explained on the basis of a wide difference in the incidence of the acute infectious diseases. It is a common belief that their incidence is much higher in the northern countries and states, and that they act to bring on the metabolic diseases. In order to show that this difference is not sufficient to serve as an important factor in determining the death rates for the metabolic diseases and angina pectoris, table 9 is presented. Only the mean death rates by groups of states are

TABLE 8.—Deaths from Angina Pectoris per 100,000 Population in Various Countries

Country	Mean Rate	Period of Years	Recent Rate	Year
Switzerland	16.0	1925
United States.....	14.7	1927
Canada	10.6	1923-6	12.3	1926
Scotland	8.7	1923-8	11.7	1928
Jamaica	8.9	1923-6	10.5	1927
New Zealand.....	7.4	1924-8	9.4	1928
England and Wales.....	6.0	1924-8	9.4	1928
Cuba	8.8	1922-5	8.9	1925
Spain	8.1	1923-6	8.0	1926
Australia	6.3	1924-7	7.8	1927
Chile	6.7	1927-8	7.2	1928
Union of South Africa.....	6.7	1923-6	6.8	1926
Hawaii	6.2	1927-8
North Ireland.....	4.2	1924-8	5.7	1928
Holland	4.8	1924-8	4.3	1928
Uruguay	4.8	1927
Italy	4.4	1924-5	4.4	1925
Colombia	4.4	1927
Irish Free State.....	2.8	1925-7	3.3	1927
Barbados	1.8	1925-7	3.0	1927
Grenada	1.7	1923-8	0.0	1928
Costa Rica.....	1.5	1927
Philippine Islands.....	1.4	1925
Panama	0.5	1923-6	1.1	1926
Ceylon	0.5	1928
Straits Settlements.....	0.5	1924-8	0.8	1928
British Guiana.....	0.4	1924-8	0.3	1928
Haiti	0.3	1926-7	0.3	1927
Nigeria	0.0	1926-7

given here. Pneumonia (all forms), acute and chronic nephritis and acute rheumatic fever were taken as representative acute infectious diseases. From the table it is seen that no significant difference in the death rates from these diseases exists in the different regions of the United States.

COMPARISON OF THE DEATH RATES FOR THE WHITE AND THE COLORED POPULATIONS

In table 10 it is seen that the death rate for pernicious anemia, etc., is lower in the Negro than in the white population, but with the acute infectious diseases and tuberculosis, the reverse is the case. This fact is strong evidence against the theory that acute infections are major

DIABETES MELLITUS

THE COLLOIDAL OSMOTIC PRESSURE OF THE BLOOD *

I. M. RABINOWITCH, M.D.

WITH THE TECHNICAL ASSISTANCE OF MISS MARY BEARD

MONTREAL, CANADA

The primary purpose of this investigation was to attempt to find the cause of wide discrepancies met with occasionally between the cholesterol content of the blood and the clinical picture in diabetes mellitus. Theoretical considerations led to a physicochemical study of the blood of such patients. The results obtained appear to be not only of clinical, but of biologic, interest in general.

Determination of the cholesterol content of blood plasma has been a routine procedure in the diabetic clinic of the Montreal General Hospital for a number of years.¹ As with all other laboratory tests, with the accumulation of data and their correlation with the clinical states, anomalous results are met with that cannot be accounted for by technical error. For example, high cholesterol values may be found in the absence of conditions with which they are usually associated in diabetes (severe diabetes, acidosis, ingestion of food of high sterol content, pregnancy, infections, nephritis, disease of the biliary passages, etc.). In searching the literature for a possible explanation of these unexpectedly high values, attention was drawn to a recent observation by Fishberg.² This author demonstrated an intimate relationship between the colloidal osmotic pressure of blood and its lipid content.

It has been known for some time that lipemia may result from, or be associated with, lowering of the concentration of blood proteins. Striking clinical examples are chronic nephritis with edema, so-called nephrosis and hemorrhage. All of these conditions have one feature in common, namely, anemia, and lipemia has been attributed to the latter by lowering oxidation or loss of blood lipase. In a discussion of this phase of the subject, however, Fishberg aptly pointed out that, though loss of red blood cells may be a contributing factor in the production of lipemia, it cannot be the only or the most important one, since in pernicious anemia—a condition exhibiting at times most severe grades of anemia—lipemia is the exception rather than the rule. As a matter of fact, one

* Submitted for publication, May 5, 1930.

* From the Department of Metabolism, the Montreal General Hospital.

* This work was done with the aid of a grant from Mr. Julian C. Smith of Montreal and a Governor of this hospital.

1. Rabinowitch, I. M.: *Canad. M. A. J.* **17**:171, 1927.

2. Fishberg, E. H.: *J. Biol. Chem.* **81**:205, 1929.

diseases in our southern states may well be caused by laxity or errors of diagnosis on the part of the medical profession in this area. There is no direct proof that such is not the case. However, the European data supply valuable evidence that the differences in death rates north and south are real and not faults in diagnosis, for surely Italy, with metabolic disease death rates similar to those of our southern states, compares favorably with the countries of northern Europe in the diagnostic ability of its medical profession.

The lower death rate for the metabolic diseases in rural districts may suggest to some the likelihood of laxity of medical diagnosis in the country districts, but in England and Wales the country rates are higher than the urban rates. Although the fact is recognized that crude death rates can be no more reliable in general than are the death certificates sent in by the physicians, I see no valid objection to their use for comparative purposes in different areas. Perhaps the greatest factor of error which should be kept in mind is the difference in the distribution in age and life expectancy of the population in different countries. Diabetes and angina pectoris are diseases of the more advanced ages, and would therefore be less prevalent in countries having a shortened mean life span. However, exophthalmic goiter and Addison's disease show their maximum death rate at considerable earlier ages, so that this factor of shortened life expectancy would influence them much less; and still they show the same geographic differences as do diabetes, pernicious anemia and angina pectoris. Mathematical treatment of the problem may well show the exact importance of the climatic factor.

From the data presented there is a strong suggestion of climatic suppression of the metabolic diseases in those tropical and subtropical areas where other metabolic functions are also lowered by the heat. The consumption of oxygen, the blood pressure and the expenditure of energy in general are lowered, resulting in a lessening of the metabolic strain, so that the exhaustive or overstimulative diseases of metabolism appear with less frequency. It is of especial interest that Japan and northern China are found to be similar to the tropics in this characteristic. Although their winter is severe and stimulating, it cannot be sufficient to counterbalance the severe depressive influence of the prolonged moist heat of their tropical summer.

The part played by differences in diet is impossible of evaluation at present. It is significant, however, to note that Americans going to China and continuing on practically unchanged dietary standards, show a distinct fall in blood pressure within two years, while Chinese coming to America show a rise. Attempts are in progress to correlate climatic differences with differences in as many phases of body metabolism as possible. The next article will deal with the relation of climate to conception rates.

attributed to the proportional decrease of protein. More recently, Fishberg² made similar observations. The effect of dilution on colloidal osmotic pressure is shown in table 1 and graphically recorded in charts 1 and 2. In their original forms, the values were expressed differently by the various authors; the protein concentrations were recorded in terms of protein and protein nitrogen, and the osmotic pressure was expressed in terms of centimeters or millimeters and as serum and water. The data were, therefore, recalculated in terms of millimeters and as total osmotic pressure and osmotic pressure per gram of protein. It will be noted that

TABLE 1.—*Effects of Dilution of Blood on Osmotic Pressure*

Verney			Mayrs			Fishberg		
Protein, per Cent	Osmotic Total	Pressure* per Gm. Protein	Protein, per Cent	Osmotic Total	Pressure per Gm. Protein	Protein, per Cent	Osmotic Total	Pressure† per Gm. Protein
9.37	498	53	7.87#	402	51	7.21	353	49
7.00	336	48	7.09	348	49	6.39	301	47
6.56	324	49	6.30	290	46	5.77	283	48
6.37	295	46	5.51	247	45	5.05	219	43
6.31	282	45	4.72	202	43	4.32	169	39
6.25	275	44	3.93	157	40	3.61	106	29
6.19	292	47	3.15	118	37	2.89	75	26
5.57	200	36	2.36	78	33	2.16	29	13
4.60	171	37	1.57	43	31			
4.50	158	35	0.79	24	35			
4.37	149	34	8.12§	401	49			
4.19	136	32	5.69	229	40			
3.87	129	33	4.06	146	36			
3.81	133	35	3.25	112	34			
3.56	117	33	2.44	81	33			
3.44	115	33	1.62	50	31			
3.34	108	32	0.81	24	30			
3.12	74	24						
2.75	66	24						

* Mm. water.

† Mm. serum or plasma.

Mixed blood (normal).

§ Individual blood (normal).

as the dilution increases, not only does the total colloidal osmotic pressure fall, but the pressure per gram of protein also decreases.

Explanation of the decrease of colloidal osmotic pressure with alteration of the relative proportions of the different forms of protein appears simple. Since osmotic pressure depends on the number of particles, and since both the particles of fibrinogen and globulin are larger than those of albumin, with preponderance of the former in a given amount of protein solution, one would expect a fewer number of molecules in a given volume and therefore a lower pressure per gram of protein. Explanation of the decrease of pressure per gram of protein with simple dilution, but without alteration of the relative proportions of albumin, globulin and fibrinogen, is much more difficult. Verney suggested, since

of the characteristics of this disease is that fat depots are well filled. On the basis of bleeding experiments in animals, Fishberg concluded that the important factor in the production of lipemia in the aforementioned conditions is loss of blood proteins, and suggested that the lipoids are mobilized in an effort to compensate for the decreasing osmotic pressure exerted by the proteins.

A not uncommon association with the aforementioned high cholesterol values is edema. The latter may manifest itself clinically in four ways: (a) puffiness of the eyelids, (b) pitting of the skin on pressure, (c) no obvious edema but rapid gain of body weight out of all proportion to food (caloric) intake or (d) a stationary body weight in spite of a diet of low caloric content.³ Among diabetic patients who are not taking insulin, the commonest cause of edema (excluding heart and kidney disease) is ingestion of large quantities of salt, either as table salt or in foods of high salt content. In diabetic patients treated with insulin, there may be an additional factor, namely, "insulin edema."⁴ In connection with these observations, it is interesting here to note that Boyd,⁵ in a study of the blood cholesterol in juvenile diabetes, found that high values for blood cholesterol were usually associated with cases of hydremia. No data with regard to the protein contents of the bloods in these cases are recorded.

In view of these observations, the possibility that high values for cholesterol may at times be a compensatory phenomenon resulting from dilution of blood has to be considered. Simple estimation of total protein would appear sufficient to test this possibility. A complicating factor, however, is the fact that the colloidal osmotic pressure of the blood appears to depend not only on the total protein content, but also on (a) the relative proportions of the different forms of protein (albumin, globulin and fibrinogen) and (b) the degree of dilution of the blood. A brief observation with regard to the last named phenomenon is necessary since the standards employed in this investigation were dependent on it.

Starling⁶ first demonstrated that serum protein exerts an osmotic pressure. In 1926, working independently, Mayrs⁷ and Verney⁸ showed that when a sample of plasma was diluted with Ringer's solution, the observed fall of colloidal osmotic pressure was greater than could be

3. With regard to conditions (c) and (d), the term edema merely implies retention of water; the fluid may be within the cells or extracellular.

4. Rabinowitch, I. M.: *Canad. M. A. J.* **17**:685, 1927.

5. Boyd, Gladys L.: *Blood Cholesterol in Diabetic Children*, *Am. J. Dis. Child.* **38**:490 (Sept.) 1929.

6. Starling, E. H.: *J. Physiol.* **19**:312, 1896.

7. Mayrs, E. B.: *Quart. J. Med.* **19**:273, 1925-1926.

8. Verney, E. B.: *J. Physiol.* **61**:319, 1926.

are not in a molecular degree of dispersion, and therefore do not conform to Avogadro's law. Since it is the number of particles that determines the magnitude of the osmotic pressure, it would appear that with dilution of blood plasma there is greater hydration or aggregation, resulting in a smaller number of particles per unit of volume. This, however, is unlikely, since, as Svedberg stated, serum proteins tend to disaggregate into smaller particles on dilution.

Whatever the explanation may be, the fact remains that with dilution of serum or plasma, the colloidal osmotic pressure per gram of protein diminishes. Assuming the rate of change of pressure with respect to the concentration of protein to be proportional to the actual osmotic

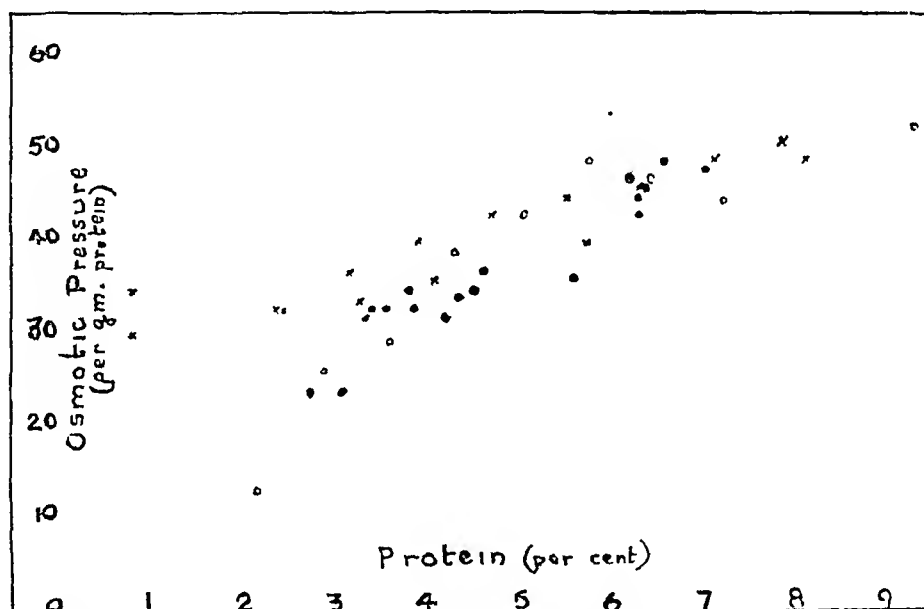


Chart 2.—Effects of dilution of blood proteins. The solid circle indicates results of Verney; the cross, those of Mayrs and the open circle, those of Fishberg.

pressure, Fishberg applied the differential equation $\frac{dp}{dv} = ap$, in which p indicates the reciprocal of the colloidal osmotic pressure, v , the reciprocal of the protein concentration and a , a constant depending on the total concentration of the proteins. In other words, $p = e^{av}$. Striking agreement was found between observed and calculated values.

In view of the foregoing observations, a series of patients exhibiting edema manifested by any one of the four signs already referred to were collected. In each case, the analyses of the blood included determinations of sugar, cholesterol, total protein and colloidal osmotic pressure.

Colloidal osmotic pressure was estimated according to the plan outlined by Mayrs;⁷ in addition, aseptic precautions were taken as much as possible, since as Verney⁸ pointed out, bacterial growth in either the serum or the dialysate may result in a decrease of pressure. The pressures are recorded in terms of millimeters of plasma, since in this inves-

the molecular volume of colloidal particles is comparatively large, that one may be dealing with a solution in a state analogous to that exhibited by a gas when highly compressed. In analogy, with van der Waal's equation of a gas, he found that the equation $p(v-b) = k$ in which p indicates osmotic pressure of the proteins, v , the reciprocal of protein nitrogen and b a constant, held for dilution of plasma up to 50 per cent of the original concentrations; in other words, the osmotic pressure of

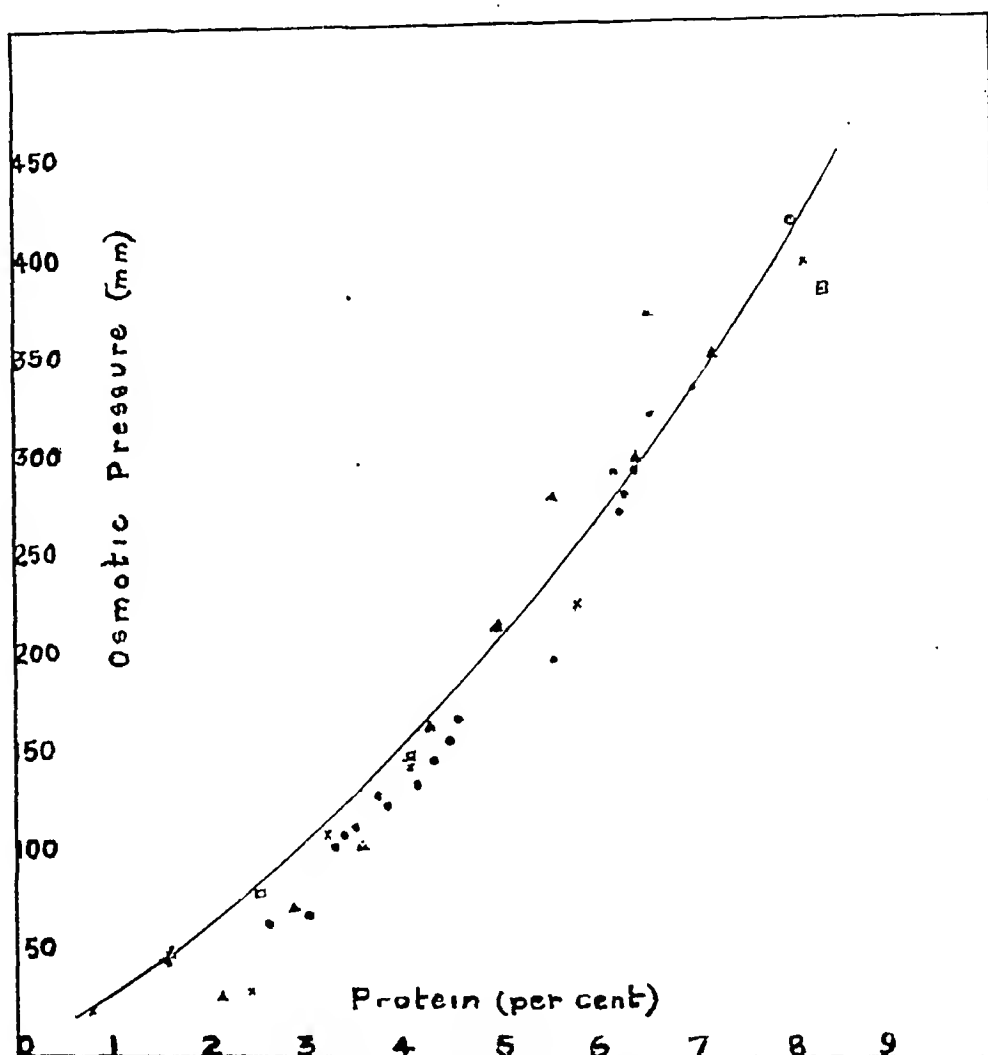


Chart 1.—Effects of dilution of blood proteins. The solid circle indicates results of Verney; the triangle, those of Fishberg; the cross, those of Mayrs (one blood); the line, those of Mayrs (mixed blood); the dot within the circle, those of Moore and Roaf; the dot within the square, those of Krogh and the star, those of Starling.

plasma proteins reacts to their dilution in a matter such as would be expected of a nonionized colloidal solution in which the colloidal particles occupied an effective volume as large as 50 per cent of the original.

It may here be noted that colloidal solutions belong to a class in which the values for osmotic pressure are less than those obtained with gram molecular solutions, namely, 22.4 atmospheres. These particles

It will be noted that the values tend to be slightly lower than the standards, but that the average difference is about 5 per cent. As Mayrs pointed out, however, though such graphs as the one employed may be found to be similar when obtained from the blood of normal persons, the levels may differ slightly. Small deviations must, therefore, not be stressed. Regardless, however, of the standards employed, there appears to be no reason for deviations to occur in a certain direction in one group of persons more frequently than in another merely from the operation of the laws of chance; and it may here be pointed out that the observations made in this paper are based on the deviations rather than on absolute values.

Though all of these subjects had some form of edema already mentioned, it will be noted that the protein concentrations, with the exception of those in nos. 8, 16 and 28, did not differ from the accepted normal values (Bodansky,¹¹ Van Slyke,¹² Wu,¹³ Plimmer¹⁴ and Hawk.¹⁵ The

TABLE 3.—*Protein-Cholesterol Relationships*

Number of Observations	Protein, per Cent	Cholesterol, per Cent		
		Low	High	Average
2.....	6.00	0.219	0.277	0.248
4.....	6.01 - 6.50	0.238	0.396	0.286
8.....	6.51 - 7.00	0.222	0.427	0.324
11.....	7.01 - 7.50	0.232	0.574	0.365
3.....	7.51 - 8.00	0.302	0.426	0.354
4.....	8.01+	0.333	0.427	0.377

one subject (no. 8) with a definitely low protein had marked insulin edema. It therefore appears that though each subject had some edema, it was, apparently, not due to lowering of concentration of blood proteins. The high cholesterol values, therefore, do not appear to be the result of a compensatory phenomena, that is, the result of an effort to maintain a constant colloidal osmotic pressure.

These conclusions may be drawn from another observation. In table 3 are shown the relationships between the cholesterol and protein values. The protein values are grouped from low to high according to their concentrations, and their corresponding low, high and average

11. Bodansky, M.: *Introduction to Physiological Chemistry*, New York, John Wiley & Sons, 1927.

12. Van Slyke, D. D., and others: *Proc. Soc. Exper. Biol. & Med.* **20**:320, 1922-1923.

13. Wu, H.: *J. Biol. Chem.* **51**:33, 1922.

14. Plimmer, R. H. A.: *Practical Organic and Bio-Chemistry*, New York, Longmans, Green & Company, 1920.

15. Hawk and Bergeim: *Practical Physiological Chemistry*, Philadelphia, P. Blakiston's Son & Company, 1926.

tigation absolute values were not sought. The important information was the relationship between normal and pathologic blood and, as Mayrs pointed out, the necessary details, in order to express the osmotic pressure in terms of millimeters of water, would involve a much greater error than may be introduced by the densities of the various samples. All analyses were made at room temperature (18 C.), and readings were made eighteen hours after the bloods were exposed to dialysis. The technic involved in this determination is by no means simple. It has all of the difficulties inherent in work on membrane permeability in general. The greatest source of difficulty is the preparation of membranes of uniform permeability. In spite of this, when there is rigid adherence to details the error involved, according to Mayrs, ranges between 1 and 5 per cent.

The standards of colloidal osmotic pressure for given concentrations of total protein were the same as those employed by Mayrs in his work

TABLE 2.—*Effect of Dilution of Plasma on Colloidal Osmotic Pressure*

Plasma	Protein, per Cent	Colloidal Osmotic Pressure		
		Actual (a)	Expected* (c)	a/c × 100
Undiluted	6.62	290	312	92.9
80%	5.30	212	228	93.0
60%	3.98	146	155	94.2
40%	2.63	93	90	103.3
20%	1.32	37	40	95.5

* The expected values were obtained from chart 1. For statistical analysis the standards obtained from the continuous line in chart 1 will be referred to, hereafter, as the "expected" values; whereas, those experimentally determined will be referred to as the "actual" values.

on pathologic processes of the kidney.⁷ Proof of the validity of these standards may be found in chart 1, in which are recorded, in addition to the data of another series of analyses by Mayers on a normal person, the observations of Verney,⁸ Fishberg,² Starling,⁹ Krogh⁹ and Moore and Roaf.¹⁰ The continuous line represents the standards used in this investigation and the dot line the data of the other authors referred to. The close agreement, particularly in the range of concentrations of protein met with clinically, is obvious.

It is obvious that unless the permeabilities of the membranes in these experiments approximated those by which the aforementioned standards were obtained, the data would hardly be comparable. Therefore, in order to test permeability, six samples of normal plasma were mixed together. The mixture was then diluted with Ringer's solution, and the diluted samples were tested with regard to their colloidal pressures with the results shown in table 2.

9. Krogh, quoted by Fishberg (footnote 2).

10. Moore and Roaf: *Biochem. J.* 2:34, 1907.

From the foregoing data, it would, also, appear that diabetic patients with lipemia, as shown by a high content of blood cholesterols, tend to have higher colloidal osmotic pressures than do normal persons. If this conclusion is correct, it appears, as will be shown presently, that the observation made is of some clinical importance. To make more certain of this conclusion, the data were treated statistically.

In view of the small number of observations, the subjects were divided into three groups only, according to the cholesterol data. The average ratios of actual to expected colloidal osmotic pressure were calculated for each group, and the significance of these averages were judged by their probable errors. The results are shown in table 5. It will be noted that the ratio of the difference between the means of the

TABLE 5.—*Relationship Between Actual to Expected Osmotic Pressure and Cholesterol*

Actual Expected Osmotic Pressure*	Cholesterol, per Cent		
	—0.3	0.81-0.40	0.41+
Mean	105.0	113.2	117.0
σ.....	6.7	4.1	3.8
PE M.....	1.32	0.83	1.26
PE Δ... ..		1.54	1.50
Δ			
PE Δ		5.1	2.5

* The symbol σ indicates standard deviation; $PE\ M = \left(\frac{0.674}{\sqrt{n}} \right)$, probable error of mean; Δ = difference between means, and $PE\Delta = \left(\sqrt{(M_1)^2 + (M_2)^2} \right)$, probable error of differences between means.

different groups to the probable errors of their differences was such as to warrant the conclusion with reasonable certainty that the observations were not the results of operation of the laws of chance.

An obvious difficulty in the interpretation of the foregoing results is that it has been assumed that cholesterol concentrations parallel total lipoids. However, such parallelism has been shown to be the rule rather than the exception among diabetic patients, though among children hypercholesterolemia and lipemia are not, according to Boyd,⁵ necessarily associated. Recently, however, Joslin¹⁶ showed that though the quantity of fatty acid was tripled, the cholesterol was only doubled. According to this observation, the lipemia in diabetes is probably greater than indicated by the cholesterol alone; in other words, lack of parallelism not only does not minimize the value of these results, but enhances them.

16. Joslin, E. P.: The Treatment of Diabetes, ed. 4, Philadelphia, Lea & Febiger, 1928.

cholesterol values are recorded. If the cholesterol values in these cases were due to a compensatory phenomenon, one would expect that as the total proteins decreased the cholesterol would increase. As a matter of fact, it appears that the cholesterol increased rather than decreased with increasing protein concentration.

TABLE 4.—*Ratios of Actual to Expected Colloidal Osmotic Pressures of Serum in Thirty-Two Cases of Diabetes Mellitus*

No.	Hospital No.	Per Cent			Osmotic Pressure (Mm. Serum)		
		Protein	Cholesterol	Sugar	Actual (a)	Theoretical (b)	$\frac{a}{b} \times 100$
1	7076-29	7.00	0.222	0.149	330	340	94
2	G.	7.17	0.240	0.119	393	348	113
3	73-30	8.31	0.416	0.140	497	440	113
4	7448-28	8.04	0.333	0.385	496	420	118
5	3953-29	6.91	0.537	0.208	405	332	122
6	2391-29	7.34	0.321	0.137	384	363	106
7	1312-29	7.08	0.232	0.333	373	345	108
8	Buch.	5.16	0.277	0.322	242	220	110
9	S. F.	6.73	0.308	0.156	333	320	104
10	6679-29	7.87	0.335	0.222	476	400	119
11	3953-29	6.65	0.427	0.201	363	313	116
12	7434-29	6.56	0.228	0.200	302	308	96
13	6000-29	7.17	0.427	0.087	414	348	119
14	3964-26	7.27	0.450	0.625	434	358	122
15	7447-29	6.74	0.273	0.059	358	320	112
16	7274-29	6.05	0.238	0.084	292	273	107
17	6038-22	8.14	0.333	0.204	493	425	116
18	1795-26	7.98	0.426	0.333	460	415	111
19	Rey.	7.35	0.500	0.149	431	365	118
20	3432-27	8.15	0.427	0.227	456	426	114
21	Dow.	7.35	0.304	0.126	405	365	111
22	McL.	7.61	0.302	0.188	429	383	112
23	2373-29	7.35	0.303	0.143	416	365	114
24	6037-29	7.43	0.326	0.123	418	370	113
25	See exp. 13	7.09	0.333	0.095	407	345	118
26	7420-29	6.13	0.268	0.125	287	280	102
27	7202-29	6.83	0.292	0.120	376	330	114
28	76-30	6.13	0.241	0.040	297	280	106
29	147-30	6.39	0.396	0.166	333	295	113
30	131-30	5.69	0.219	0.196	245	250	98
31	147-30	6.56	0.302	0.112	336	308	109
32	197-30	7.09	0.574	0.066	407	345	118

A possible fallacy in the interpretation of the foregoing data is that though the total protein values were normal, there may have been alterations of the relative proportions of albumin, globulin and fibrinogen. Though separate analyses of these three constituents of blood protein were not made, the data on the colloidal osmotic pressure oppose this view. It will be noted (table 4) that in the majority of cases the ratios of actual to expected pressures are not only above unity, but greater than can be accounted for by the percentage of error inherent in the technic.

content of the serum were also estimated. The chlorides were determined by the satisfactory method of Wilson and Ball.¹⁷ The combined data are shown in table 7.

It will be noted in each case that at some time during the period of observation the blood was diluted according to the values of (a) the plasma-cell ratios and (b) the total protein concentrations. Allowing a technical error of 5 per cent, the actual and expected colloidal osmotic pressures, however, agreed fairly closely. Dilution of blood with saline, therefore, does not appear to result in compensatory lipemia. The serum chloride, it will be noted, though not great, was definitely greater after

TABLE 7.—*Effects of Ingestion of Large Quantities of Salt*

Protein, per Cent	Cholesterol, per Cent	Sugar per Cent	Osmotic Pressure			Plasma Cells	NaCl per Cent			Weight, Pounds	No.
			Actual (a)	Theoretical (b)	a — b 100						
6.13	0.268	0.125	319	280	114	0.85	0.520	Dec. 27	Foreed fluids with salt		7420/29
5.86	0.326	283	260	109	Dec. 28		= 116½	
5.69	0.241	265	250	106	Dec. 30	30 Gm. NaCl	= 118¾	
4.49	0.228	0.125	176	182	97	2.12	0.566	Dec. 31		= 127¼	
5.43	0.232	0.212	221	235	94	1.21	0.552	Jan. 2		= 127¼	
5.95	0.241	0.125	273	265	103	1.14	0.560	Jan. 3		= 125¼	
6.56	0.228	0.232	329	305	108	1.00	0.550	Dec. 27			7434/29
6.83	0.214	315	328	96	Dec. 28		= 124	
6.90	0.232	340	330	103	Dec. 30	64 Gm. NaCl + 16,500 cc. water	= 134	
5.25	0.183	207	225	92	1.41	0.640	Dec. 31		= 154	
5.95	0.169	0.200	262	267	98	1.23	0.555	Jan. 2		= 148¾	
6.12	0.169	0.208	283	275	103	1.03	0.566	Jan. 3		= 139	
6.74	0.273	0.059	355	320	111	0.92	0.566	Dec. 31	15 Gm. NaCl	= 155¼	7447/29
6.13	0.225	0.181	274	280	98	0.82	0.575	Jan. 2		= 154	
6.06	0.189	0.117	284	273	104	1.14	0.590	Jan. 3		= 156½	

ingestion of salt than can be accounted for by technical error inherent in the method employed.

There is another possible criticism of all of these observations, since, according to some workers, particularly German, blood proteins exert an insignificant osmotic pressure, if any. These authors believe that serum attracts water through a membrane of collodion because the proteins seek to imbibe water and be more hydrated; the condition is looked on as inhibition. Professor Mayrs¹⁸ is also of the opinion that the blood lipoids can exert little osmotic pressure. They, as he pointed out, could do so only if in solution, and even then the amounts present

17. Wilson, D. W., and Ball, E. G.: J. Biol. Chem. **79**:221, 1928.

18. Personal communication.

When shown these data, Professor Mayrs pointed out another possible difficulty with regard to their interpretation. As ratios of albumin to globulin were not determined, the possibility of high ratios must be considered, since relatively large amounts of albumin would tend to raise the colloidal pressure regardless of the lipid content of the blood. In routine practice over a number of years, this laboratory has had occasion to determine such ratios, and none has ever been found to be high. Alterations of the relative proportions of albumin and globulin have invariably decreased rather than increased these ratios. In order, however, to exclude this objection as much as possible, four subjects were reexamined with the results shown in table 6.

These observations were made between three and four months after the first examination. This probably accounts for the different values obtained. It will be noted, however, that the phenomenon observed was the same, namely, higher ratios of actual to expected colloidal osmotic pressures associated with hypercholesterolemia. High ratios of albumin

TABLE 6.—*Results of Reexamination of Four Subjects*

Subject No.	Total Protein, per Cent	Albumin Globulin	Cholesterol, per Cent	Osmotic Pressure		
				Actual (a)	Expected (e)	a/e × 100
3953-29	7.34	2.13	0.490	476	365	130.4
7448-28	7.62	1.86	0.520	484	384	113.0
3964-26	6.84	2.24	0.427	376	328	114.6
7202-29	7.31	1.79	0.347	416	360	115.5

to globulin are therefore excluded as a possible cause of high colloidal osmotic pressure, at least in the subjects investigated.

As the subjects investigated had edema, it was considered of interest to note the effects of markedly diluting blood with salt solution and compare them with the results of bleeding experiments reported by Fishberg. For this purpose, three diabetic subjects were selected. In two cases the diabetes was active; both showed marked emaciation. On admission, one patient (7420-29) had, in addition to glycosuria, marked acetonuria; the other (7434-29) had glycosuria only. The third subject (7447-29) had mild diabetes and was well nourished, but had gangrene of one of the feet. In each case, well salted broth was given at hourly intervals for a day. Each subject reacted differently to the experiment. The first (7447-29) took little salt and gained only 1 pound (0.5 Kg.) in twenty-four hours; the second (7420-29), a little more enthusiastic, took more salt and gained 9½ pounds (4.3 Kg.) during the same period. The third case (7434-29) was a classic. This subject took 64 Gm. of salt, drank 16,500 cc. of water and gained 22 pounds (10 Kg.) in twenty-two hours. In each of these cases, in addition to the data obtained in the other cases, plasma-cell ratios and the sodium chloride

in or near coma tend to develop anuria. The latter, however, is not a constant observation. If raised colloidal osmotic pressure is a factor and if lipemia is the cause, one would expect to find some relationship between lipemia and anuria. As this was an afterthought, the degrees of anuria found in the past cannot be determined quantitatively, since no exact measures were made of the volume output of urine. Data on the urea are, however, available, as the determination of this blood constituent is a routine in all of our cases of coma. It appears reasonable to assume that, in the average, the more marked the anuria, the greater would be the concentration of urea in the blood, though a number of variables must also be considered, such as the duration of the coma, etc.

TABLE 8.—*Systolic and Diastolic Blood Pressures of All Subjects*

Subject No.	Age, Years	Blood Pressure		Subject No.	Age, Years	Blood Pressure	
		Systolic	Diastolic			Systolic	Diastolic
1	60	142	74	17	56	180	95
2	43	120	78	18	56	145	90
3	54	140	80	19	51	150	92
4	61	150	90	20	50	165	100
5	59	160	90	21	49	128	76
6	26	140	82	22	52	138	80
7	43	165	94	23	41	145	86
8	31	130	76	24	37	114	70
9	58	142	82	25	16	180	64
10	70	195	100	26	43	104	66
11	59	160	90	27	11	165	90
12	56	125	78	28	19	130	65
13	16	180	64	29	43	115	60
14	63	140	88	30	22	110	80
15	52	128	66	31	43	115	60
16	34	110	74	32	18	118	84

In table 9, are shown the necessary data to test this idea. Here are recorded the last thirty cases of diabetic coma of which our records are complete. In each case are recorded the age of the patient, the presence or absence of renal damage, the white blood cell count, blood sugar, blood urea and cholesterol and the degree of coma. The classification of the latter is arbitrary but serves for practical purposes and is as follows:

<i>Degree</i>	<i>State</i>
1	Drowsy
2	Semiconscious
3	Unconscious, but respond to painful stimuli
4	Completely unconscious

The data are grouped in table 10 in order to demonstrate relationship, if any, between the various phenomena. Briefly, it will be noted

do not appear to be great enough to account for the values found. This author makes the interesting suggestion that the phenomena observed might be explained by the lipoids reducing the permeability of the colloidin membranes. There is experimental basis for this suggestion; for example, Krogh obtained exceptionally high colloidal osmotic pressures by using membranes of low permeability. A control experiment suggested was to deproteinize diabetic and normal specimens of blood and compare the osmotic pressures of the remaining fluids. An objection to this procedure, however, is that during deproteinization one could hardly avoid altering the physical condition of such blood. Another suggestion was to compare the colloidal osmotic pressure of normal plasma plus lecithin emulsion in Ringer's solution with normal plasma plus Ringer's solution alone. With this experiment, the lecithin was not found to exert any osmotic pressure. Again, it may be observed that one can hardly simulate the physical state of blood lipoids with artificially prepared lecithin mixtures. As will presently be observed, however, the actual mechanism involved, that is, whether one is dealing with osmotic pressure, inhibition pressure or altered membrane permeability, is irrelevant; the fact that because of lipoids water is attracted or held in the sac is the important clinical consideration, as the following observations suggest, providing an analogy may be drawn between capillary walls and colloidin membranes.

If the prevalent view of urinary excretion is correct, that is, if hydrostatic pressure must overcome the resistance of some other form of pressure in the capillaries before glomerular filtration can occur, it follows that in diabetic patients with lipemia a greater hydrostatic force must be exerted if urine is to be excreted. Increased intra-arterial pressure, whether due to injection of epinephrine or continuous sympathetic stimulation, is alleged to produce arteriosclerosis in animals. One can hardly compare the marked resistance offered to the circulation in the latter types of experiments with the small amount possible as a result of increased colloidal osmotic pressure. Continued, however, over a long period of time, is this responsible for the marked incidence of cardiovascular disease in diabetes? Apropos of this suggestion, the data in table 8 are of interest. These subjects were selected for this investigation, not because of their blood pressures, but because of their edema and blood cholesterol. It is, therefore, interesting to note that of these thirty-two subjects, eighteen, an incidence of 56 per cent, had hypertension—an incidence too great even for diabetic subjects. (No. 28 is assumed to have hypertension, since a hemoglobin of 130 is too high for a boy 19 years of age.)

The relationships found between cholesterol (or lipemia) and anuria in diabetic coma are also suggestive. As is well known, diabetic patients

exists in such a state as to exert its own osmotic pressure. This, it may be observed, fits in with the anomalously high colloidal osmotic pressure in hypertension quoted by Verney⁸ from Govaerts (*Bull Acad. roy. de méd. de Belg.*).

SUMMARY AND CONCLUSIONS

Though this investigation failed so far as finding an explanation for certain high cholesterol values occasionally met with in diabetic blood is

TABLE 10.—*Relationships Between Blood Sugar, Cholesterol, Urea Nitrogen, Leukocytes and Severity of Coma in Thirty Cases of Diabetic Coma*

Average	Blood Sugar			
	—0.4	0.41 – 0.80	0.81+	
Cholesterol.....	0.566	0.637	0.707	
Urea nitrogen.....	30	36	52	
White blood cells.....	15,000	18,000	19,000	
Cholesterol				
	—0.4	0.41 – 0.80	0.81+	
Sugar.....	0.417	0.579	0.622	
Urea nitrogen.....	17	37	51	
White blood cells.....	20,000	18,000	15,000	
Urea Nitrogen				
	—25	26 – 50	51+	
Sugar.....	0.445	0.726	0.720	
Cholesterol.....	0.385	0.740	0.813	
White blood cells.....	17,240	16,000	22,000	
Leukoeytes				
	—10	11 – 25	25+	
Sugar.....	0.421	0.604	0.429	
Cholesterol.....	0.500	0.728	0.462	
White blood cells....	22,000	43,000	35,000	
Severity				
	1	2	3	4
Sugar.....	0.505	0.572	0.500	0.781
Cholesterol.....	0.586	0.572	0.535	0.903
Urea nitrogen.....	36	29	27	70
White blood cells.....	14,200	20,000	15,000	22,000

concerned, a new phenomenon was observed. It is suggested that though there is relatively little direct evidence, the sum of all available data (clinical and laboratory) tends to support the view that in diabetes with lipemia there is constantly exerted in the capillaries a colloidal pressure greater than the normal. To overcome the latter for purposes of renal excretion, a greater hydrostatic pressure is required; this increased pressure, though relatively small, when continued over a long period of

that urea nitrogen and cholesterol were related. This conclusion is, it may be pointed out, based on averages. It is, therefore, a statistical conclusion and may, or may not, and need not necessarily, apply to any particular subject. Though there are, as stated, a number of variables to consider, these data tend to support the idea that in coma with lipemia

TABLE 9.—*Diabetic Coma*

No.	Hospital No.	Age, Years	Degree of Coma	Urine		Blood				Comment
				Albu- min	Casts	Sugar, per Cent	Choles- terol, per Cent	Urea, Nitrogen, Mg. per 100 Ce.	White Blood Cells	
1	197-30	18	2	+	+	0.464	0.574	15	34,000	
2	-30	20	2	+	+	0.625	0.241	11	27,400	Blood obtained after insulin
3	6419-29	11	1	+	+	1.200	0.637	35	26,200	
4	7420-29	44	1	+	+	0.277	0.577	18	5,600	Blood obtained after insulin
5	6123-29	22	3	+	+	0.769	0.640	32	24,000	
6	5041-29	55	1	+	+	0.416	0.669	71	12,200	
7	4525-29	65	2	+	+	0.333	0.214	22	28,500	Lobar pneumonia
8	4451-29	17	3	+	+	0.500	0.416	22	21,600	
9	4392-29	31	3	+	+	0.416	0.370	20	18,400	
10	4349-29	40	1	+	+	0.265	0.660	32	10,200	
11	4062-29	34	1	+	+	0.500	0.428	11	8,450	White blood cells on day after coma
12	2020-29	26	1	+	+	0.769	0.578	35	22,000	
13	431-29	49	2	+	+	0.277	0.341	15	No white blood cells
14	254-29	69	1	+	+	0.476	0.402	31	10,000	
15	7411-28	15	2	+	+	0.625	0.980	38	10,100	
16	6738-28	23	4	+	+	1.100	1.158	36	16,000	Before admission; no coma on admission
17	6535-28	17	1	+	+	0.454	1.190	62	16,800	
18	5996-28	35	3	+	+	0.434	0.297	17	8,600	
19	6453-28	48	2	+	+	0.400	0.577	24	11,200	
20	5728-28	23	4	+	+	0.590	1.330	49	18,200	
21	5517-28	36	3	+	+	0.285	0.925	42	7,600	
22	1516-28	28	2	+	+	0.555	0.584	21	18,200	
23	121-28	76	2	+	+	0.769	1.140	82	15,800	
24	6244-27	30	1	+	+	0.555	0.428	13	7,850	
25	4569-27	27	3	+	+	0.584	0.562	28	14,600	
26	4203-27	2½	4	+	+	0.526	0.593	94	38,200	
27	2490-27	47	2	+	+	1.100	0.500	35	16,400	
28	958-27	58	4	+	+	1.000	0.483+	101	18,400	Before coma
29	356-27	35	1	+	+	0.333	0.613	36	19,400	
30	336-27	48	1	+	+	0.295	0.624	49	22,400	

a greater hydrostatic pressure of blood is required to induce glomerular filtration.

In this connection it also is interesting to note that, according to Westphal, cholesterol is more readily extracted from blood with ether in diabetes and hypertension than in hypercholesterolemia associated with infections, pregnancy and nephrosis; in other words, there is further suggestive evidence that in diabetes and hypertension, cholesterol

THE EFFECTS OF INTRAVENOUS INJECTIONS OF FOREIGN PROTEIN ON PEPTIC ULCER *

JACOB MEYER, M.D.

AND

LOUIS B. KARTOON, M.D.

CHICAGO

The present study is an attempt to interpret the effects of intravenous injections of nonspecific foreign proteins on patients with peptic ulcer. We studied the effect on gastric secretion, hoping to obtain data that might be of value in elucidating the genesis of pain in gastric and duodenal ulcer. We also wish to record our observation of the therapeutic effects of foreign protein in peptic ulcer.

Previous observers reported improvement of symptoms, especially relief from pain, following injections of protein. Pribram¹ noted that in forty-two of seventy-seven patients pain stopped immediately at the end of treatment. A month after the injections were stopped, thirty-eight remained free from pain. At the end of eight months, there was subjective cure in thirty-two cases, but in seven of these, although there was no pain, there were pyrosis and a feeling of weight. Pribram analyzed the gastric juice in thirty-one of his cases. Under the influence of injections of protein, the acidity became normal in eighteen; in seven it decreased without becoming normal, and in six the hyperchlorhydria increased. Kalk² studied the curve of secretion in seventeen patients; in seven the acidity and duration of secretion remained unchanged; in four there was a slight decrease, and in only one a marked decrease. Von Friederich³ found that treatment with foreign protein had little effect on the acidity. Martin⁴ recently reported his experiences, and remarked that "The first change one notices during treatment is a marked decrease in pain." In a group of seventeen cases observed immediately

* Submitted for publication, April 10, 1930.

* From the Medical Service of the Cook County Hospital.

1. Pribram, B. O.: Parenterale Reizbehandlung des Magen und duodenal Geschurs, *Med. Klin.* **18**:958 (July 23) 1922.

2. Kalk, H.: Erfahrungen mit protein-korper Therapie des Ulcus duodeni und ventriculi, *Klin. Wchnschr.* **2**:1310, 1923.

3. von Friedrich, Ladislaus: Protein Therapie der peptischen Geschure, *Arch. f. Verdauungskr.* **34**:75, 1925; Zur Frage der protein Therapie des Magen und duodenal Geschur, *München. med. Wchnschr.* **72**:458, 1925.

4. Martin, Lay: Peptic Ulcer: The Effect of Parenteral Injections of Purified Milk Proteins on Symptoms and Progress, *Arch. Int. Med.* **43**:299 (March) 1929.

time probably has the same effect as more marked intracapillary pressure exerted over a short period of time. In animals the latter, when produced either by injection of epinephrine or by sympathetic stimulation, is alleged to cause arteriosclerosis. Is this, therefore, a cause of the marked incidence of cardiovascular disease in diabetes? The data are recorded, in order that the theory may be tested by others with similar facilities available.

ADDENDUM

During the course of further experiment and since this paper was submitted for publication, an interesting observation was made with regard to the colloidal osmotic pressure of lipemic blood which is of sufficient interest to be added to this report.

As is well known, the plasma of diabetic blood may, while still fresh, be clear, in spite of a fat content of from 2 to 3 per cent or more; but when such blood is exposed to ordinary room temperature over a period

TABLE 11.—*Effects of Physical State of Blood Fat on Colloidal Osmotic Pressure*

Date	Total Protein	Total Fat	Cholesterol	Colloidal Osmotic Pressure		
				Actual	Expected	Actual Expected
May 21.....	6.50	1.90	0.433	342	300	114.0
May 22.....	6.43	1.82	0.421	285	295	96.6

of from twelve to twenty-four hours, it may become cloudy, and the cloudiness is due to fat globules. Why one lipemic blood should be turbid and another clear is imperfectly understood. Bloor, I believe, was the first to record this phenomenon and termed it "masked lipemia." This author also suggested that it depends on the physical state of the fat.

The interesting observation with regard to colloidal osmotic pressure is that in one such case of masked lipemia accidentally observed recently the ratio of actual to expected colloidal osmotic pressure was high when the plasma was clear, whereas it was normal the following day, when the plasma became turbid on standing at room temperature.

These observations would suggest that when the blood was first withdrawn and the plasma was clear, the lipoids were in solution and could then exert an osmotic pressure; whereas on standing, when the blood became cloudy the fat was in suspension and, therefore, could not exert an osmotic pressure. The first idea that occurred to me was that the blood while standing at room temperature had undergone proteolysis. Though slight proteolysis did occur, it does not entirely explain the decrease of osmotic pressure (table 11).

TABLES SHOWING RESULTS OF FRACTIONAL GASTRIC ANALYSES IN PEPTIC ULCER BEFORE AND AFTER INTRAVENOUS
INJECTION OF FOREIGN PROTEIN

TABLE 1.—*Acidity Reduced with Relief from Pain—Cases 1, 2, 3 and 4; Case 2, Typhoid Vaccine Used*

	Control Fractional		After Typhoid Vaccine, 500,000,000 Temperature 99.5 F.				After Typhoid Vaccine, 1,000,000,000 Temperature 100 F.				After Typhoid Vaccine, 1,200,000,000 Temperature 101 F.				After Typhoid Vaccine, 1,500,000,000 Temperature 102.6 F.				After Typhoid Vaccine, 1,500,000,000 Temperature 101.4 F.				Fractional 9 Days After Last Injection	
	Free	Total	24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		Free	Total
			Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total				
Empty.....	30	41	21	31	50	63	20	31	26	39	45	52	41	47	50	61	27	33	0	18	20	30
Aspir.....	96	101																						
1st.....	42	51	32	44	11	21	18	25	0	22	30	36	20	27	15	22	18	24	12	16	12	16	15	24
2d.....	46	54	68	77	22	28	33	40	30	38	38	44	15	23	26	34	32	40	20	28	20	28	18	16
3d.....	60	71	42	58	55	63	55	63	60	71	50	59	40	52	50	57	43	51	31	40	30	41	16	25
4th.....	62	72	48	59	50	60	45	56	52	61	56	61	49	61	61	69	52	60	35	42	35	42	11	19
5th.....	70	83	60	72	42	51	45	59	60	73	57	63	64	76	44	52	38	44	56	65	56	64	30	38
6th.....	65	80	30	43	36	43	68	77	59	66	60	68	50	59	50	63	20	35	20	29	25	36

TABLE 2.—*Acidity Reduced with Little or No Relief from Pain; Case 7, Gonococcus Vaccine Used*

	Control Fractional		After Gonococcus Vaccine, 600,000,000 Temperature 100.2 F.				After Gonococcus Vaccine, 800,000,000 Temperature 102.2 F.				After Gonococcus Vaccine, 1,200,000,000 Temperature 101 F.				After Gonococcus Vaccine, 1,500,000,000 Temperature 103.4 F.			
			24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours	
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total
Empty.....	60	66	26	38	Not obtained		22	36	50	59	34	49	18	34	24	37	32	46
1st.....	46	56	16	25	40	49	10	19	29	38	15	28	19	26	18	25
2d.....	72	79	14	27	42	53	11	22	40	56	45	54	25	34	21	29
3d.....	83	96	28	39	43	51	38	46	62	69	22	35	35	42	30	42
4th.....	89	98	40	53	42	52	60	68	61	70	36	42	45	56	26	35
5th.....	62	69	36	44	20	33	71	84	70	78	52	62	42	51	42	51
6th.....	64	70	29	37	52	68	79	87	51	63	46	54	32	40	29	38

after treatment, there was an increase in acidity in five, an approximate constancy in nine and a true decrease in three. Of twenty-eight cases, eight were observed after a period of from four to eighteen months, and among these, there was an increase of acid in two, an approximate constancy in two and a decrease in four. It is interesting to note that of the four patients showing a decreased acidity, three are reported as clinically well, and an operation was performed on the fourth. The two patients who showed a "constancy of acidity" are also reported as being clinically well, while of the two with an increase in acidity, one was operated on and showed a healed duodenal ulcer and the other was reported as being worse.

PRESENT STUDIES

Eleven patients were studied. The clinical diagnosis of peptic ulcer (gastric or duodenal) was made from a careful analysis of the history, the symptoms and the physical signs, such as localized tenderness, positive roentgen shadows and positive gastric analysis and analysis of the stools.

The patients selected for study were on a general ward diet, except that meat was excluded. They were not confined to rest in bed, but were allowed to walk about the ward as they desired.

A control fractional gastric analysis was made on each patient in addition to the Ewald test meal, which was given as a routine procedure.

An intravenous injection of foreign protein was given the following day. The first dose contained from 500,000,000 to 800,000,000 gonococcus or typhoid vaccine (we found that gonococcus vaccine gave a much more severe reaction than typhoid vaccine, and therefore we used it in the greater number of cases). If the reaction following the initial dose was severe, the dose on subsequent injections was the same. If the reaction was mild or moderate, the dose was increased to 1,000,000,000, then to 1,500,000,000 and finally to 2,400,000,000. Five or six injections were given to each patient. The interval between each injection was from five to seven days.

Fractional gastric analysis was made on each patient twenty-four and forty-eight hours following each injection, and whenever possible from one to two weeks after the final injection. The temperature was recorded every four hours on the day of the injection and for two days after.

Roentgenograms and fluoroscopic examinations were made before the first and after the last injection. Analysis of the stools were made throughout the entire period of observation.

Tables 1 to 4 illustrate the changes in acidity of the gastric juice following intravenous injections of foreign protein. Our results showed

TABLE 5.—Acidity Unchanged in Control

Control	After Gonococcus Vaccine, 500,000,000 T. normal			After Gonococcus Vaccine, 900,000,000 Temperature 102.2 F.			After Gonococcus Vaccine, 1,200,000,000 Temperature 102.4 F.			After Gonococcus Vaccine, 1,500,000,000 Temperature 101.4 F.			After Gonococcus Vaccine, 1,500,000,000 Temperature 100.4 F.			Fractional 5 Days Later						
	24 Hours		48 Hours	24 Hours		48 Hours	24 Hours		48 Hours	24 Hours		48 Hours	24 Hours		48 Hours							
	Free Total	T. 101.8 F.	Free Total	Free Total	T. normal	Free Total	Free Total	Free Total	T. 102.2 F.	Free Total	Free Total	Free Total	Free Total	T. 102.4 F.	Free Total		Free Total					
Empty.....	75	85	35	45	43	53	63	75	Not obtained	30	39	35	43	65	72	Not obtained	30	49	45	55	46	53
1st.....	31	43	25	36	23	28	15	27	..	36	43	32	40	50	61	..	42	53	36	42	38	49
2d.....	50	58	35	45	26	56	23	36	..	63	72	48	59	74	82	..	49	60	43	50	56	64
3d.....	74	86	36	42	27	52	30	41	..	61	70	62	71	60	71	..	52	64	60	68	63	72
4th.....	48	59	34	46	65	73	60	69	..	50	62	70	82	60	69	..	60	71	93	86	60	74
5th.....	53	60	39	50	51	62	65	72	..	62	70	62	70	56	63	..	62	72	66	74	71	80
6th.....	64	73	32	39	43	55	65	72	..	41	58	70	79	52	61	..	48	57	72	80	56	66

TABLE 3.—*Acidity Unchanged—Pain Relieved—Cases 5, 8 and 9; Case 5, Gonococcus Vaccine Used*

Control	After Gonococcus Vaccine, 600,000,000 Temperature 101.6 F.				After Gonococcus Vaccine, 800,000,000 Temperature 101.8 F.				After Gonococcus Vaccine, 1,200,000,000 Temperature 102 F.				After Gonococcus Vaccine, 1,500,000,000 Temperature 103 F.				After Gonococcus Vaccine, 2,000,000,000 Temperature 101.6 F.				Fractional 2 Weeks After Injec- tions			
	24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours					
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total				
Empty.....	33	49	10	20	15	28	30	41	50	59	42	54	20	28	15	20	55	65	68	79	36	47	25	34
1st.....	38	47	38	46	32	40	26	32	40	48	58	66	68	73	55	61	68	76	74	82	68	79	40	50
2d.....	50	61	56	64	40	47	38	42	52	59	69	77	73	80	60	68	77	84	70	79	56	62	46	53
3d.....	52	63	52	61	49	57	61	70	45	56	63	72	67	74	51	62	73	80	72	80	63	73	48	55
4th.....	45	57	44	52	35	62	54	61	66	73	84	98	56	66	62	69	70	77	79	88	71	80	41	52
5th.....	32	36	58	79	60	71	51	62	62	70	79	85	40	48	57	66	48	60	78	87	73	82	49	63
6th.....	12	18	75	86	33	37	60	72	72	81	62	68	51	60	52	63	56	63	67	81	73	86	40	49

TABLE 4.—*Acidity Increased—Pain Relieved—Case 10, Gonococcus Vaccine Used*

Control	After Gonococcus Vaccine, 500,000,000 Temperature 103.4 F.				After Gonococcus Vaccine, 600,000,000 Temperature 99 F.				After Gonococcus Vaccine, 800,000,000 Temperature 104 F.				After Gonococcus Vaccine, 800,000,000 Temperature 103 F.				After Gonococcus Vaccine, 800,000,000 Temperature 102 F.							
	24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours		24 Hours		48 Hours					
	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total	Free	Total				
Empty.....	12	21	0	6	4	16	4	16	Not obtained	4	16	Not obtained	No free acid in any speci- men	0	6	6	16	Refused to be aspirated	0	12	0	6	6	14
1st.....	0	14	0	8	0	8	0	8	..	0	8	0	8	5	14	..	0	9	6	14
2d.....	18	26	9	14	6	12	7	18	..	4	13	4	13	11	18	..	8	20	0	9
3d.....	19	29	11	19	10	18	8	18	..	20	28	20	28	19	28	..	12	26	10	19	23	39
4th.....	15	27	10	18	9	15	11	19	..	32	47	32	47	26	34	..	23	39	16	29	16	29
5th.....	21	29	0	11	0	11	0	9	..	43	52	43	52	21	30	..	20	32	18	27	20	32
6th.....	16	25	8	21	5	19	9	15	..	38	40	38	40	26	32	..	16	22	15	26	16	22

observers (Hurst, Ginsburg and his associates, Carlson and Ivy⁶). Pribram said that in addition to its other effects foreign protein acts on the vagus and sympathetic system, causing relaxation of the spasm. He noted that following the injection of novoprotein, epinephrine causes no change in the pulse rate and blood pressure, and he concluded from this that the excitability of the nervous system is diminished by the injection of protein. Both Holler⁷ and Pribram⁸ reported that pylorospasm is abolished by foreign protein, and that the decrease in spasm is so marked that a stenosis, which was thought to be due to anatomic deformity, disappeared. Von Friedrich does not believe that the improvement in gastric function is due to relaxation of the pyloric spasm, but that during an attack of pain, the musculature of the stomach is in a condition of hypotonia, comparable to that of a myocardium in a condition of decompensation. Under the influence of novoprotein, the condition became

TABLE 6.—Showing Return to Normal Acidity with Normal Temperature

	Given Gonococcus Vaccine, 500,000,000					
	Control		Temperature 102 F.		Temperature Normal	
			24 Hours		48 Hours	
	Free	Total	Free	Total	Free	Total
Empty.....	67	80	11	24	62	71
1st.....	41	54	7	16	21	34
2d.....	88	93	20	34	34	42
3d.....	57	69	36	47	63	71
4th.....	38	44	41	49	80	89
5th.....	60	72	38	45	63	76
6th.....	78	86	39	47	73	84

normal and effective, like that of a myocardium under the influence of digitalis. This hypothesis, however, is contradicted by the observations of Müller and Petersen,⁹ who showed that nonspecific protein causes a

6. Hurst, A. F.: The Sensibility of the Alimentary Canal, London, Oxford University Press, 1911. Ginsburg, H.; Tumpowsky, I., and Hamburger, W. W.: Contributions to the Physiology of the Stomach: XXXV. The Newer Interpretation of the Gastric Pain in Chronic Ulcer, J. A. M. A. **67**:990 (Sept. 30) 1916. Carlson, A. J.: Am. J. Physiol. **45**:81, 1917. Ivy, A. C.: Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

7. Holler, Gottfried: Ist eine organische Vaguserkrankung die Ursachen des Ulcus ventriculi chronicum beim Menschen, Wien. klin. Wchnschr. **34**:223, 1921.

8. Pribram, B. O.: Protein Therapie und chirurgische Therapie des Magenschurs, Klin. Wchnschr. **2**:2112, 1923.

9. Müller, E. F., and Petersen, W. F.: Ueber die Wirkung der Protein-korperinjektion auf den Mageninnervation, München. med. Wchnschr. **74**:531, 1927.

that the gastric acidity was decreased in five patients, unchanged (or very little change) in four and increased in one.

In four patients a reduction in acidity was observed, and this was associated with relief from pain. In one patient (case 7, table 2) a definite reduction in acidity occurred but no relief from pain and no improvement. In the patients in cases 5, 8 and 9 (table 3), there was no change in the gastric acidity, but the pain was relieved and the patients were improved. In the patient in case 10 (table 4), who was suspected of having carcinoma, and who had initial low acidity, the acidity was increased and the pain was relieved for from twenty-four to forty-eight hours. In a patient with gastrojejunal ulcer, the acidity was reduced, but complete studies were not made.

COMMENT

Meyer, Cohen and Carlson⁵ studied the effects of fever on gastric secretion in dogs and noted a marked depression in acidity during the fever. Foreign protein was used in these experiments. These observations were conducted during the febrile period, and it was noted that there was a marked diminution in the free, total hydrochloric acid and volume of gastric juice, and that on the following day, when the animals were free from fever, the secreting response was normal. In a measure, our present observations on patients coincide with the observations on dogs. We were unable to obtain gastric analysis at the height of fever (in some cases as high as 104.2 F.), but occasionally the rise in temperature persisted after a reaction, as in case 9.

We were inclined to believe that a possible explanation of the immediate relief from pain was the diminution in the gastric acidity and gastric secretion occurring at the height of the fever. Assuming that this diminution occurred in all cases in which the patients were treated with foreign protein, the return to a normal acidity in a period of from twenty-four to forty-eight hours with relative freedom from pain would be evidence against acidity as the cause of pain. More convincing evidence against acidity as a prime factor is the presence of pain following a definite reduction in acidity (all other causes of pain, such as cholecystitis, chronic appendicitis, etc., having been ruled out). This, as we have pointed out, was well illustrated by the patient in case 7. In a like manner, we find it difficult to explain the relief from pain following a definite increase in acidity (case 10).

That gastric tonus and gastric hunger contractions are the important factors in the mechanism of pain in ulcer is a view held by many

5. Meyer, Jacob; Cohen, Seymour J., and Carlson, A. J.: The Effect of Fever on Gastric Secretion, *Arch. Int. Med.* **21**:354 (March) 1918.

CLINICAL OBSERVATIONS

A clinical analysis of the therapeutic effects is necessarily limited by many factors that enter into the control of patients, particularly of the class referred to the Cook County Hospital. Emphasis is therefore placed on the fact that the present therapeutic report is one of observations of clinical progress rather than end-results. It is also particularly emphasized that the period of observation was not sufficient to warrant conclusions as to end-results.

We feel it important to call attention to the following facts:

Relief from Pain.—As many other observers, we also find that the relief from pain following injections is a striking feature. The relief from pain is apparently not dependent on the severity of the constitutional reaction or the degree of temperature. The analgesic effect was noted in every instance, in periods varying from eighteen hours to several months after injections. Two patients showed striking relief following the first injection for the entire period of observation; two showed moderate relief after the first injection (of these, one had a carcinoma of the stomach). Pribram was of the opinion that the intravenous route is the best. It would seem, however, from the results of others, that subcutaneous injections produce similar therapeutic effects. Our excuse for using the intravenous method was our interest in observing the effect on the acidity. We did not encounter any untoward effects.

The Effect on Patients with Definite Bleeding.—Four of the patients studied gave a history of profuse bleeding. One patient had severe melena for six months and again three weeks before admission; one patient with gastrojejunal ulcer had a constant 4 + blood reaction in the stool, and one patient had a carcinoma of stomach with a constant 4 + blood reaction in the stool. One patient had a definite history of hematemesis. None of these might be considered as having acute gastric hemorrhage. It did not appear that the constitutional reaction or the possible changes in the tissues about the ulcer, which are said to occur after injections of protein, were of such a nature as to produce an increase in bleeding; on the contrary, blood disappeared from the stools during and after treatment in all of the patients except the one for whom a diagnosis of carcinoma was made. This was particularly striking in the patient with a gastrojejunal ulcer.

Effect on Roentgen Deformities.—As we remarked, all of our patients showed a definite duodenal or gastric defect fluoroscopically and by x-ray films before we accepted them for study. Fluoroscopy was performed in every instance at the end of the course of treatment, but we were unable to note any marked change in the gastric defects. In one instance, the gastric defect seemed smaller. No case showed complete disappearance of the deformity.

diminution of the gastric contractions in man. Likewise, Meyer and Carlson,¹⁰ while studying hunger and appetite during fever in dogs, showed that there was a complete absence of hunger contractions following injections of sodium nucleinate. Meyer and Carlson were of the opinion that the fever or the toxins appear to induce a lowering of the vagus tone and thus lead to a cessation of the hunger contractions.

In view of these observations, we are of the opinion that a similar lowering of vagus tonus and a diminution of gastric tonus and gastric contractions occur in man following injections of protein and are important factors in the relief from pain.

Is the relief from pain, following the injection of foreign protein, associated with the improvement of the circulation in the stomach and the increased vascularity about the ulcer? Clinicians have noted the relief from pain in peripheral vascular disease, as in thrombo-angiitis obliterans following the intravenous injection of foreign protein. In these cases the relief from pain is due to increased vascularity and improved collateral circulation. Is it likely that the relief from pain in ulcer is due to a similar phenomenon? We believe this to be the case. We wish to present the hypothesis that pain from ulcer is associated with variations and disturbances in the blood supply in and about the ulcer. It is generally assumed that the ingestion of food relieves the pain from ulcer, because it diminishes tonus and neutralizes acidity. We wish to advance the hypothesis that pain is diminished because the ingestion of food increases the general vascular supply of the stomach, particularly about the area of the ulcer. Consequent on this increased vascular supply there is a diminution in tonus and spasm and therefore relief from pain. The return of pain in from one-half to one hour or longer after food, we explain thus: as digestion proceeds, there is an increase in vigor of the peristaltic activity; this increased activity depletes the vascular bed of the rugae of the stomach, particularly in the ulcer-bearing area, and results in local asphyxia, edema, spasm and pain. This hypothesis, it seems to us, offers a reasonable explanation of the rhythmic character of pain in peptic ulcer. Likewise it presents an explanation of pain from ulcer independent of the degree of acidity. We explain the relief from pain obtained by the ingestion of alkalis by the observations of pharmacologists¹¹ that dilute solution of alkalis may act as an irritant to the gastric mucosa, improving the circulation and thus relieving the pain and distention.

10. Meyer, Jacob, and Carlson, A. J.: Hunger and Appetite in Fever, *Am. J. Physiol.* **44**:222 (Sept.) 1917.

11. Cushny, A. R.: *Pharmacology*, ed. 9, Philadelphia, Lea & Febiger, 1928, p. 572.

THE BOLTZ TEST IN URINALYSIS *

ARTHUR T. BRICE, JR., B.A.

WASHINGTON, D. C.

This test was first described by Boltz¹ in 1923 as a simple and specific spinal fluid test for dementia paralytica. Grossman,² in 1925, and Harris,³ in 1926, essentially confirmed this report, Grossman adding that the white of an egg also gives a positive reaction. Walker and Sleeper,⁴ in 1927, questioned the accuracy of the previous results, and offered convincing evidence, mainly of a chemical nature, that the test is not specific. They stated that a positive reaction is due to a reaction between an aldehyde and tryptophan. In 1928, Myerson and Halloran⁵ reported that they had found that in spinal fluid a positive Boltz reaction is obtained whenever there has been an increase in protein from whatever cause, the degree of positivity corresponding closely with the quantitative increase in protein. They stated that it is not a specific test for dementia paralytica, and that it is positive in spinal fluid in the presence of protein; but they offer no conclusive evidence that the positive reaction in spinal fluid is due to proteins alone, or that proteins play the principal part in the reaction. They recommend the use of the acetic anhydride of Powers, Weightman and Rosengarten, which contains a relatively large amount of aldehyde, present as an impurity. The work of the authors mentioned indicates that the positive reaction results from the presence of an amino-acid, presumably tryptophan.

It came to my attention by accident that this test might be applied directly to the urine, and this report is based on the examination of 167 normal and 525 pathologic specimens.

TECHNIC

(a) Place in a small glass test tube 1 cc. of the filtered or centrifugated specimen to be examined.

(b) Add 0.3 cc. of acetic anhydride, preferably a brand high in aldehyde content, from a pipet, a drop at a time, with shaking.

* Submitted for publication, May 17, 1930.

* From the Clinical Laboratory of the McLeod Infirmary, Florence, S. C.

1. Boltz, O. H.: *Am. J. Psychiat.* **3**:111, 1923-1924.

2. Grossman, S.: *J. Ment. Sc.* **21**:439, 1925.

3. Harris, J. S.: *Brit. M. J.* **1**:136 (Jan. 23) 1926.

4. Walker, B. S., and Sleeper, F. H.: *J. Lab. & Clin. Med.* **12**:1048 (Aug.) 1927.

5. Myerson, A., and Halloran, R. D.: *J. Nerv. & Ment. Dis.* **68**:155 (Aug.) 1928.

Terminal Results.—One patient (case 2) had a recurrence one week after a course of five injections. He was operated on, and a shallow gastroduodenal ulcer was found situated at the pyloric ring and extending to the duodenum. In another patient, symptoms recurred six weeks after the course of intravenous treatment. In two patients, no symptoms were noted seven and six months, respectively, after injections, and in another, nine months after treatment. Seven months after the injection, the x-ray film in the last patient still showed the duodenal defect.

CONCLUSIONS

1. Relief from pain during treatment for peptic ulcer obtained by intravenous injections of foreign protein is independent of changes in acidity.
2. We believe that the diminution in gastric tonus and contractions which occurs following injections of foreign protein is an important factor in the relief from pain.
3. The increased vascularity in the stomach and in the capillary bed in and about the ulcer is the important factor in relief from pain.
4. We wish to advance the hypothesis that rhythmic pain in ulcer is due to rhythmic variations and disturbances in the vascular bed in and about the ulcer, associated with digestive peristaltic activity.
5. Nonspecific protein is to be considered only as an adjunct in the treatment for peptic ulcer.

The single positive specimens from controls 3 and 7 were very faintly positive by the test. Control 5, who showed six positive specimens of twenty taken during a period of sixty-one days, reported that he had suffered from a mild nephritis several years previously. Control 6 was a rather neurasthenic person, who stated that he believed himself to be suffering from some metabolic insufficiency of an unknown nature, as he was entirely unable to gain weight though he habitually ate large quantities of food.

I concluded from this series that in the normal human man on an average diet, no amino-acid detectable by the Boltz test should be eliminated in the urine.

PATHOLOGIC OBSERVATIONS

The pathologic series comprised examinations of 525 specimens: 161 were from medical cases, of which 35 per cent were found to have positive Boltz reactions; 332 were from surgical cases, of which 33 per

Normal Control Series

Control	Total Specimens Examined	Specimens Having Positive Boltz Reactions
1 Laboratory worker (male) . . .	32	0
2 Physician (male)	25	0
3 Intern (male)	23	1
4 Physician (male)	21	0
5 Physician (male)	20	6
6 Intern (male)	19	4
7 Physician (male)	14	1
8 Laboratory worker (male)	6	0
9 Intern (male)	4	0
10 Intern (male)	3	0

cent were positive; 32 were from obstetric cases, of which 16 per cent were positive. The highest positive observation was 72 per cent in the group of specimens from patients with degenerative diseases of the kidneys. Another highly positive observation among the medical groups was 46 per cent of the specimens from patients with acute infections. The highest positive observation in the surgical groups was in specimens from cases of appendicitis, the percentage being 42. The small number of specimens from uncomplicated obstetric cases showed no positive observations.

The high incidence of the positive Boltz reaction of 72 per cent of all specimens from patients with degenerative diseases of the kidneys would seem to indicate that the primary significance of the positive test is that the kidneys have been affected. In this group the positive Boltz reaction was always accompanied by the finding of albumin. This was far from the case, however, in considering the observations in the pathologic group as a whole. The high incidence of positive Boltz reactions of albumin-free specimens—46 per cent of all the positive Boltz reactions, or 15 per cent of all the specimens examined—clearly suggests

(c) Add 0.8 cc. of concentrated sulphuric acid, from a pipet, a drop at a time, with shaking.

(d) Let the tube stand at room temperature under observation for five minutes.

The positive reaction is indicated by the appearance of a light lilac to deep purple color. Occasionally, in weak positive reactions, the positive color may appear within the five minute period and subsequently be obliterated by the darker colors due to the reaction of other substances in the urine. Occasionally, in strongly positive reactions the positive color may not appear before the expiration of some minutes, owing to the darker colors produced immediately by the reaction of other substances in the urine. In strongly positive specimens the purple color may be so dark as to require dilution of the preparation with water in order to differentiate the purple from possible dark browns or blacks. The prescribed five minutes of the test is a valid test period, as positive specimens have been shown to hold the positive color for several hours. The test with urine is practically impossible to read by any of the artificial lights with which I have experimented up to the time of writing.

EXPERIMENTAL OBSERVATIONS

I have been unable to produce a positive Boltz reaction with aqueous, alcoholic or ethereal extracts of dehydrated beef heart powder, or with cholesterol in solution in these liquids, or with cholesterol in solution in any of these extracts of dehydrated beef heart, or with cholesterol in solution in urine.

I have checked Grossman's positive observation with the white of an egg. I have also produced positive Boltz reactions with aqueous solutions of trypsin and with casein.

The substance producing the positive Boltz reaction in urine is destroyed by bacterial growth. In weakly positive specimens, it may disappear in a few hours. In strongly positive specimens, it may still be demonstrated after several days. The substance may be preserved in urine by the addition of a sufficient amount of any of the following reagents to inhibit bacterial growth: chloroform, ether, phenol. The positive reaction is interfered with by the addition of an excess of phenol. Formalin in the proportion of 1 cc. of the 40 per cent commercial product per ten cubic centimeters of the specimen immediately destroys the substance. The substance is precipitated and preserved by the addition of mercuric chloride.

NORMAL OBSERVATIONS

The specimens reported on in the accompanying table were obtained from voluntary controls—physicians, interns and laboratory workers. The time periods covered by the examinations ranged from one week for controls 8 and 10 to sixty-two days for controls 2 and 3. The specimens were obtained at varying hours of the day, but at intervals of at least eighteen hours. During the total period covered by the examinations, controls 2, 3, 6, 9 and 10 were on essentially the same diet; the other controls were on different diets.

ANTIBODY FORMATION IN KALA-AZAR *

H. L. CHUNG, M.D.

AND

HOBART A. REIMANN, M.D.

PEIPING, CHINA

Numerous attempts have been made to show that antibodies originate in the hematopoietic system. It has been found that stimulation of the hematopoietic system by bleeding or by other methods causes an increase in the production of demonstrable antibodies. On the other hand, injury to the blood-forming organs by overexposure to x-rays or radium or by the injection of large dose of benzene or other poisons usually results in a diminished production of demonstrable antibodies. Animals thus treated are also less immune to experimental infection. Furthermore, it has been shown¹ that patients with chronic diseases of the blood-forming organs (aplastic anemia, lymphatic and myelogenous leukemia) show little or no antibody response following the injection of various bacterial antigens.

While such evidence tends to show that the blood-forming organs play the chief rôle in the formation of immune bodies, other investigators emphasize the importance of the reticulo-endothelial system as the chief site of antibody origin. Evidence for the latter contention is not conclusive. The reports of many experiments designed to show variations in the antibody response after "blocking" the reticulo-endothelial system with various colloidal substances are conflicting. It has also been shown² that experimental typhus fever, a disease characterized by rather widespread proliferation and degeneration³ of the endothelial system without much evidence of damage to the blood-forming organs, has little or no influence on immunity or on the formation or behavior of certain demonstrable immune bodies. These results tend to reduce the importance of the reticulo-endothelial system as the chief site of antibody origin.

Further studies were made on patients with kala-azar, a disease characterized by marked proliferation of the endothelial tissue of the liver, spleen, lymph nodes and bone-marrow. In no other disease is the

* Submitted for publication, May 3, 1930.

* From the Department of Medicine, Peiping Union Medical College.

1. Rotky, H.: *Zentralbl. f. inn. Med.* **35**:953, 1914. Howell, K. M.: Failure of Antibody Response in Leukemia, *Arch. Int. Med.* **26**:706 (Dec.) 1920. Howell, K. M., and Schultz, O. T.: *Proc. Inst. Med., Chicago* **5**:52, 1924.

2. Reimann, H. A., and Wu, C. J.: *J. Immunol.* **18**:159, 1930.

3. Bauer, E.: *München. med. Wchnschr.* **63**:541, 1916. Hertzog, G.: *Centralbl. f. allg. Path. u. path. Anat.* **29**:97, 1918.

that the test may be more useful than the test for albumin to disclose early or latent conditions of the kidney, and further investigation of this possibility is to be desired.

Another inference of significance may be drawn from the following figures: Of the group of specimens taken from patients with chronic and acute infections, 32 per cent with the positive Boltz reactions were albumin-free; of the group of specimens taken from patients on whom appendectomy and miscellaneous laparotomy, including salpingectomy, had been performed, 58 per cent with the positive Boltz reactions were albumin-free; of the specimens from patients with nervous and mental diseases, 80 per cent with the positive Boltz reaction were albumin-free; in the traumatic cases, 85 per cent of the specimens with positive Boltz reactions were albumin-free. A positive Boltz reaction would therefore seem to be a significant physical observation in nervous and mental diseases and in cases of shock. Two of the cases encountered in the series were worthy of mention.

CASE 1.—J. N., came into the outpatient clinic on Sept. 29, 1929, with an undiagnosed fever. A strongly positive Boltz reaction was the only positive observation.

CASE 2.—The clinical study of the terminal case of Mr. S., admitted to the clinic on Sept. 20, 1929, yielded no information leading to a diagnosis. The strongly positive Boltz reaction in the urine was the most significant observation. Provisional diagnoses of carcinoma of the gallbladder and chronic cholecystitis complicated by lobar pneumonia were advanced, but not confirmed entirely as permission for an autopsy was refused.

SUMMARY AND CONCLUSIONS

The Boltz acetic anhydride reaction is discussed, and its application in urinalysis is reported. Results of the examination of 167 normal and 525 pathologic specimens are given.

The Boltz test is a valuable adjunct to urinalysis that demonstrates the elimination of an amino-acid.

Evidence is offered indicating that the test may be more valuable than the test for albumin to demonstrate an early or latent condition of the kidney, though further investigations are to be desired in order to make this evidence conclusive.

Evidence is offered indicating that the positive Boltz reaction in urine is of particular significance in nervous and mental cases and in shock.

usually fell off rather rapidly to 1,280 or 640, and then more slowly until at the end of two months they were 320 or 160. As in the observations reported later, the agglutinin response to *B. paratyphosus* A was usually the strongest and that to *B. typhosus* the weakest. In one person *B. paratyphosus* A agglutinin titer reached 5,120 while that for *B. typhosus* never exceeded 320 and disappeared in thirty days.

Chart 1 represents typical agglutinin titer curves in a normal subject. For convenience the chart is drawn to a different scale than chart 2, and does not emphasize the striking difference in immune response between the patients and the normal persons studied.

Agglutinin Formation in Kala-Azar.—Agglutinins for one or more of the three strains were formed in all vaccinated cases even if in low

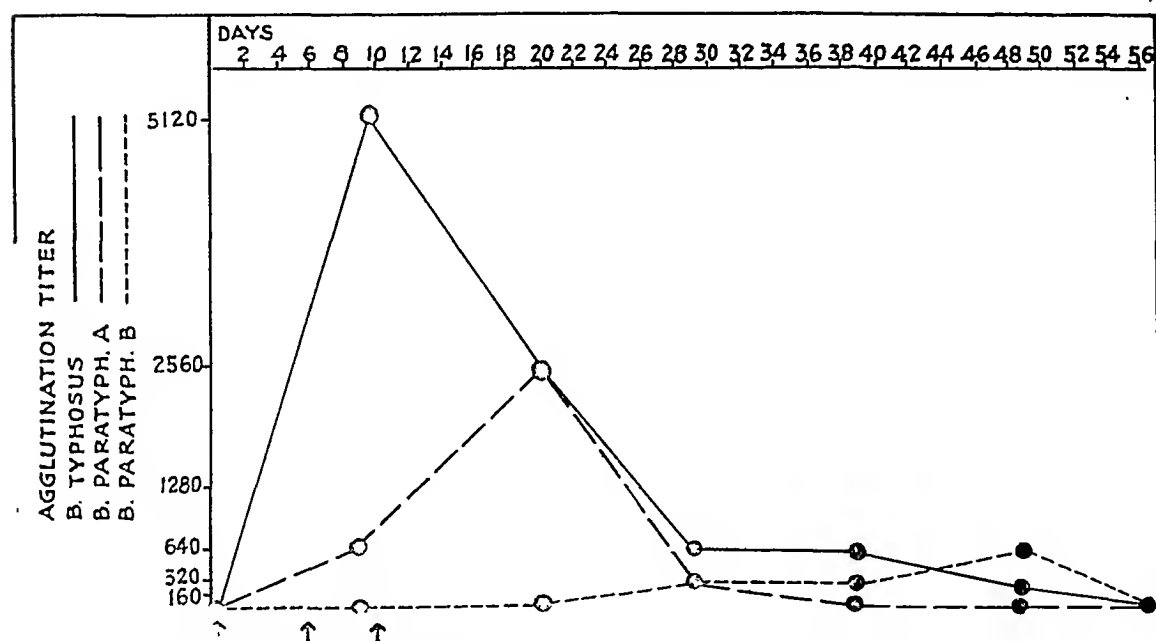


Chart 1.—The average agglutinin response in a normal subject vaccinated with triple typhoid vaccine. The ordinate is drawn to a different scale than in chart 2. The arrows indicate the time of vaccination.

titer. In four of the nine cases the titer for *B. paratyphosus* A reached 640 in two or three weeks after the first injection, and then rapidly diminished. In one case the titer reached 1,280, the highest observed in the patients with kala-azar, but rapidly fell off to 80 in three weeks. By the end of two months the titer diminished to 80 or 160 in three patients and had disappeared in five others.

The agglutinin titer for *B. typhosus* or *B. paratyphosus* B never exceeded 320 in any of the patients with kala-azar. In three cases agglutinins for *B. typhosus* failed to appear at all. At the end of two months, agglutinins for these strains were present at a titer of 80 in three patients and were not demonstrable in five others.

intensity of the endothelial reaction so great. In addition, the hemato-poietic system is also injured, as is shown by the marked anemia, leukopenia and thrombopenia that occur. There is also histologic evidence of a lack of erythropoiesis in the bone-marrow.⁴ Clinical evidence clearly indicates a marked depression of immunity. Cancrum oris and other secondary infections commonly occur and frequently terminate fatally. Studies were then made to determine the nature of the demonstrable immune response (agglutinins) to the injection of typhoid vaccine in nine Chinese patients with kala-azar. For purposes of comparison, one patient who had recovered from kala-azar a few months previously, six healthy young adults and two patients with chronic myelogenous leukemia were similarly vaccinated and studied.

METHOD

Triple typhoid vaccine containing 500,000,000 *Bacillus typhosus* and 250,000,000 each of *Bacillus paratyphosus* A and B per cubic centimeter, prepared by the National Epidemic Bureau of Peiping, was used. Subcutaneous injections of 0.5 cc., 1 cc. and 1 cc. were made at five day intervals. Blood was withdrawn for examination before vaccination, after the second vaccination and thereafter at approximately ten day intervals for two months or more. The serum was separated, and agglutination tests were performed according to the standard macroscopic technic. All patients with kala-azar were under treatment with urea stibamine and recovered during the period of observation.

EXPERIMENTAL OBSERVATIONS

In general, a striking difference in the immune response was noted between the patients with kala-azar or leukemia and the healthy subjects. The temperature was frequently increased shortly after vaccination, but no unusual effects were observed on the number of any of the blood cells in the patients with leukemia or kala-azar. In most cases the immune response to *B. paratyphosus* A was greatest and to *B. typhosus*, poorest.

Agglutinin Formation in Normal Persons.—Many studies have shown that agglutinins for typhoid bacilli in normal persons increase rapidly after vaccination, and that two weeks after the third injection they sometimes reach a titer of 10,000 or 20,000. The titer may be maintained at a high level for one or two months, then begins to decline slowly and is often still demonstrable a year or two later. In order to establish controls for the vaccine and for the technic used in the experiments on patients with kala-azar, six normal young adults were vaccinated and observed. The agglutinins for all three strains appeared promptly and rose rapidly in most instances to 5,120 but

4. Meleney, H. E.: Am. J. Path. 1:147, 1925.

The second patient was in a more serious condition, with 3,000,000 erythrocytes and 260,000 leukocytes per cubic millimeter of blood. He had been ill for one year and was declining. After vaccination the agglutinin titer in his serum for *B. typhosus* never exceeded 80 and soon disappeared entirely. Agglutinins for *B. paratyphosus* A and B failed to appear.

COMMENT

The clinical impression of diminished resistance to secondary bacterial invasion during kala-azar is corroborated by experimental laboratory evidence of a depression of the immune response to injected bacterial antigens. A similar depressed response occurred in vaccinated patients with leukemia. Although specific agglutinins were found in all cases following vaccination, they were much weaker in titer and disappeared much sooner than the agglutinins of similarly vaccinated normal controls. Both kala-azar and leukemia are diseases that affect the blood-forming organs profoundly. Therefore, since immunity and demonstrable antibody formation are depressed during these two diseases, evidence is at hand that indicates a relationship between the hematopoietic system and the formation of immune bodies. During or after recovery from kala-azar, as shown in two patients observed in this study, the normal ability to form agglutinins returns.

In spite of the numerous investigations thus far made, it still seems impossible to locate the exact site of origin of antibodies, or even to determine if an exact site actually exists. Evidence is at hand indicating that the hematopoietic system is at least an important source. It has been shown that procedures that stimulate blood formation may simultaneously increase antibody titer and that procedures that injure the blood-forming organs may cause a simultaneous depression of antibody formation. However, in many of the experiments tried and in the diseases studied, it is difficult to estimate the rôle of the reticulo-endothelial system or other systems that also may play important parts. It is difficult to gage the amount of actual harm done to the reticulo-endothelial system as well as to the hematopoietic system following overexposure to x-rays or the injection of poisons. Furthermore, in kala-azar and in leukemia the endothelial system is also profoundly affected, so that it is impossible to conclude that injury to the hematopoietic system alone is responsible for the diminished antibody formation.

CONCLUSION

There is a marked depression of the immune response to typhoid vaccination in patients with kala-azar and leukemia. After recovery from kala-azar, agglutinins are again formed normally.

Chart 2 illustrates a typical experiment. The agglutinin response to all three strains was low in this case and disappeared within thirty days after the first vaccination. A large staphylococcus abscess formed on the thigh toward the end of the disease. In spite of the abscess, no stimulation of antibodies occurred.

One patient in whom vaccination was begun during the last few days of illness and finished when his temperature was normal, showed a fairly high response (640) to all three strains after the first vaccination. Three weeks later, while the titer was diminishing, he developed acute pharyngitis and furunculosis. Immediately following this the titer for *B. typhosus* rose to 2,560 and for *B. paratyphosus* A and B to 5,120, and it was still present at 640 four weeks later.

The agglutinins of a patient included in this study who had recovered from kala-azar six months previously responded to vaccination like the normal subjects used for controls. The hospital record of another

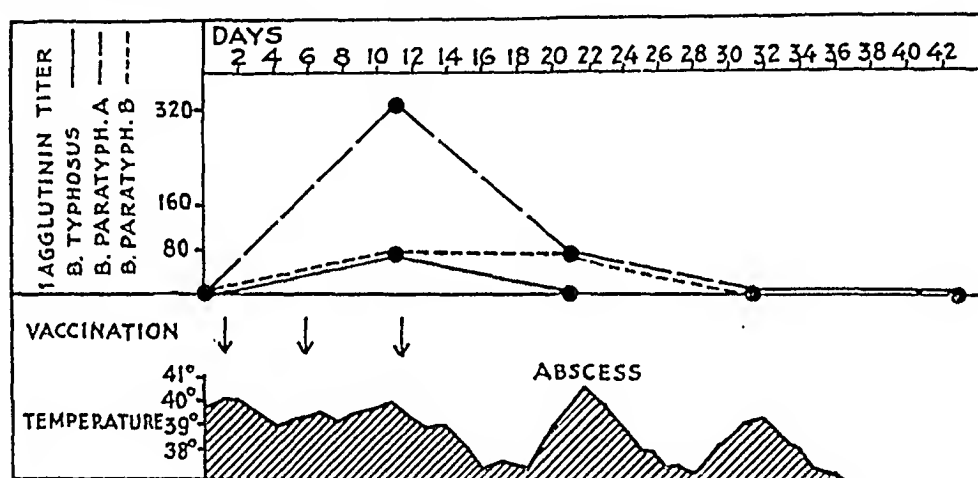


Chart 2.—The low agglutinin response and early disappearance of agglutinins in a patient with kala-azar vaccinated with triple typhoid vaccine.

patient who developed typical typhoid fever during kala-azar was found. The blood culture was positive for *B. typhosus*, but agglutinins did not appear as late as twenty-seven days after the onset.

Agglutinin Formation in Myelogenous Leukemia.—It has already been shown that during leukemia, a disease of the blood-forming organs, there is a marked depression of agglutinin response to bacterial antigens. These observations were confirmed by the results observed in two patients with chronic myelogenous leukemia included in this study. One patient had a normal erythrocyte count and a leukocyte count of 60,000, and he had been ill for two years. He had been treated repeatedly with radium. Ten days after vaccination with the triple typhoid vaccine, the agglutinin titer for *B. typhosus* and *B. paratyphosus* A reached 640. Thereafter it rapidly declined and was not demonstrable twenty days later. The agglutinin titer for *B. paratyphosus* B never exceeded 40.

proteins are detectable in tuberculosis as the result of the influence of bacterial toxins and broken-down pulmonary tissue particles. It is found that the total amount of protein may be normal or increased in tuberculosis or decreased if marked cachexia is present. The amount of globulin becomes abnormally high while the albumin reaches very low levels. The average fibrinogen content of the blood in normal persons is 0.2 per hundred cubic centimeters. Gram² reported fibrinogen values from 0.25 to 1.22 in tuberculosis.

Diminution in the number, volume and hemoglobin index of the erythrocytes may result in an increased sedimentation speed, while opposite results will cause a slower sedimentation.

Before discussing the results of the sedimentation test in tuberculosis, it is important to point out the variations of the sedimentation rate in normal blood described by many authors. The sedimentation rate is higher in infants and young children than in adults and in women than in men; it is increased during menstruation and during digestion. Variations were demonstrated by several authors in healthy persons under external application of heat and following ultraviolet ray and roentgen radiation. Some reports even show wide variations under apparently physiologic conditions at different times during the day in the same person. On the other hand, Loehr³ claimed that though such variations may occur, they usually fall within the normal range. In our work we did not find the so-called physiologic variations during a day or from day to day to have any significance concerning the result and interpretation of the test, and we believe that they do not detract from its value and can be entirely disregarded in routine clinical work. At the same time it is necessary to emphasize the fact that no correct evaluation of this test is possible unless the external or incidental factors enumerated as having a possible influence on the sedimentation rate are eliminated or discounted.

Equal emphasis must be laid on exactly controlled uniform technic, whatever method is used. It must be kept in mind that the sedimentation speed will be increased when the test is performed at high room temperature. Venous stasis and tilting of the tubes will also increase appreciably the sedimentation rate. Of the different procedures, the Westergren method was adapted with some modification as follows:

TECHNIC

Draw 3.8 per cent sterile sodium citrate solution to the 0.4 cc. mark of a 2 cc. syringe previously washed with the same solution, taking care to shake out all air

2. Gram, H. C.: On Causes of Variation in Sedimentation of Corpuscles and Formation of Crusta Phlogistica ("Size," "Buffy Coat") on Blood, *Arch. Int. Med.* **28**:312 (Sept.) 1921.

3. Loehr, Hans: *Klin. Wchnschr.* **1**:483, 1922.

ERYTHROCYTE SEDIMENTATION TEST IN TUBERCULOSIS

A STUDY OF TWO THOUSAND CASES *

ANDREW L. BANYAI, M.D.

AND

SYLVIA V. ANDERSON, B.S.

WAUWATOSA, WIS.

The recent medical literature contains numerous reports dealing with the clinical application of the erythrocyte sedimentation test, an excellent review of which may be found in a valuable study of Peterman.¹ The conclusions drawn from these works concerning its specificity, reliability and usefulness in the diagnosis and prognosis of tuberculosis are far from being unanimous. For this reason we feel that the information derived from the study of this test in 2,000 consecutive cases at Muirdale Sanatorium might be worth recording.

The phenomenon that red blood cells suspended in solutions of anti-coagulants, such as sodium citrate, potassium oxalate, hirudin or heparin, settle down with increasing rapidity in a great many pathologic conditions has been utilized in the recognition of certain diseases since 1897. The efforts of Fahraeus to detect pregnancy by means of the sedimentation test in 1918 were followed by reports from practically all branches of medicine.

Among the various explanations of the varying rate of sedimentation of erythrocytes, the following two seem to be the most plausible: (1) an increase in the fibrinogen content of the blood plasma and (2) changes in the number and size of the erythrocytes.

Red blood cells settle down very rapidly in solutions of high fibrinogen content, and several investigators have shown that in diseases characterized by fast sedimentation a definite increase in the fibrinogen content of the plasma can be found. Toxin production as it occurs in many inflammatory and destructive diseases will involve a breaking down of tissue proteins, and subsequently the products of disintegrated tissue proteins, particularly that of the lung tissue, will stimulate fibrinogen formation. One of our best coagulants used as a routine measure in the treatment for pulmonary hemorrhage is Mill's fibrogen prepared from extract of lung tissue. Changes in the amount and composition of blood

* Submitted for publication, April 10, 1930.

* From Muirdale Sanatorium.

1. Peterman, M. G., and Seeger, S. J.: Sedimentation Reaction in Children, *Am. J. Dis. Child.* **37**:693 (April) 1929.

bronchiectasis, pulmonary abscess, subacute bacterial endocarditis, rheumatic endocarditis, Pick's disease, rheumatic polyarthritis, hypertrophic arthritis, Hodgkin's disease, exophthalmic goiter, syphilis, gonococcic sepsis, Still's disease, chronic pyelitis, chronic osteomyelitis, purulent otitis media, tonsillitis, sarcoma of the tibia and aplastic pernicious anemia. It is necessary to emphasize the frequency with which rapid sedimentation occurs in many pulmonary diseases other than tuberculosis. In addition to these diseases, senile dementia, neurosyphilis, general paralysis, epilepsy, malaria, leprosy, pneumonia, Addison's disease, acute arthritis, malignant conditions in general and inflammatory conditions of the genito-urinary system have been reported by others as causing increased sedimentation. It was found that jaundice and anemias cause a retardation of the rate. Yet we had under our care a patient with aplastic pernicious anemia who showed a marked increase in the rate of sedimentation. It can be said, therefore, that an increase in sedimentation velocity does not indicate tuberculosis unless all of the conditions mentioned can be excluded. A test that changes from so many causes should be utilized with utmost caution for the diagnosis of tuberculosis.

While it is generally accepted that rapid sedimentation in itself does not necessarily indicate tuberculosis, many investigators have expressed the opinion that a normal sedimentation rate excludes active tuberculosis. On the basis of our observations we doubt that so much reliability can be placed on this test without jeopardizing diagnostic exactness and the benefits of early and appropriate treatment. Among the 2,000 patients admitted to the sanatorium with a tentative diagnosis of tuberculosis since the routine use of the sedimentation test was established at Muirdale, 128 were found who had active tuberculosis, pulmonary, extrapulmonary or both, diagnosed by physical examination and corroborated by roentgen and laboratory observations, and whose sedimentation rate on repeated examination was normal. This figure is high enough to warrant a detailed analysis of these cases.

The group includes seventy-seven male and fifty-one female patients, varying in age from 2 to 59 years, of whom eighty-nine were adults and thirty-nine were children. The proportion in the colored race was found to be much lower than that in the general population of the sanatorium. This fact has no definite explanation except an innate lessened tissue resistance against the destructive effect of the tuberculotoxins or the lack of adequate immune body formation in these patients. Out of the total number with normal sedimentation rate, eighty-one patients had had frank parenchymal lesion of the lungs, fourteen having minimal, fifty-four moderately advanced and thirteen far advanced processes. In comparison with the percentage distribution in these three stages among all our patients, as taken from the sanatorium statistics for the year 1928,

bubbles. Draw blood either directly from the patient's vein or from a tube of fresh blood. Fill the syringe to 2 cc., making the ratio of citrate to blood 1:5. Then allow a 0.1 cc. bubble of air to enter, and invert the syringe several times permitting the bubble to travel back and forth, thus mixing the blood and citrate solution. The blood is now ready to be transferred into a sedimentation tube which is a 1 cc. clear glass container, open at both ends and graduated into 100 equal parts like the barrel of a Luer tuberculin fornier. Before the tube can be used it has to be sealed at the base with a mixture of equal parts of paraffin and petrolatum melted together. The wax is packed into the tube up to where the graduation begins. The tube is held upright in a large sized rubber stopper. Let one or two drops of the blood mixture run first to the very bottom of the sedimentation tube, and the rest will follow easily without blocking the narrow opening. When the tube is full as nearly as possible to the 1 cc. mark, record the exact time, and set the interval timer to ring in fifteen minutes, when the first reading is made. Other readings follow in half an hour (from the time the test was started), one, two and twenty-four hours.

The results are recorded on a graph on which the time is indicated along the horizontal line and the percentage reading of the red blood cell level along the vertical line. To make comparison simple, a minimal normal curve, based on the sedimentation rates of eighty healthy persons, is always shown on this graph. The readings of the normal curve are 97, 95, 90, 75, 40, at the time intervals above mentioned; readings above this series are, of course, normal too. For the sake of convenience and brevity, the whole series of readings may be stated as one figure which actually represents the percentage of a test as compared with the minimal normal curve. For example, add the figures 97, 95, 90, 75, 40 given above and 3 (an arbitrary number) and divide the sum by 4; the result equals 100. Compare the normal with a test reading, 90, 75, 60, 50, 40 (add 90, 75, 60, 50, 40, 3 and divide by 4): the result is 79. In other words, this test is only 79 per cent of the normal.

Concerning its applicability in tuberculosis, the following questions should be answered:

1. Is it a specific reaction?
2. Is it an indicator of activity?
3. Is it an index to the extent and character of the tuberculous lesion?
4. Does it have any prognostic value?
5. Can it be used for the control of the course of the disease, including the detection of new foci and complications, and for judging the results of treatment?

OBSERVATIONS

It was pointed out that increased fibrinogen content of the blood, parallel with an increased sedimentation rate, may occur in a great many inflammatory conditions and in patients with malignant tumors. Of the 2,000 cases included in this study, the types of nontuberculous cases showing rapid sedimentation were as follows: pulmonary cancer, chronic unresolved pneumonia, pulmonary actinomycosis, chronic bronchitis, pulmonary syphilis, allergic asthma, pulmonary gangrene,

formation or absorption or fibrotic tissue formation. There is no doubt that whatever course the inflammatory condition takes, during its existence toxins are absorbed and are present in the blood; yet in these cases this does not effect any change detectable by the sedimentation test.

It is much more plausible to presume that the sedimentation rate in a certain number of fibrotic processes is a manifestation of less toxicity, higher resistance and a prompter defense mechanism.

As an approach toward the explanation of this exception to the apparent rule of abnormal sedimentation rate in pulmonary tuberculosis, it can be pointed out that the course and prognosis of the disease in this group was more favorable than was found in similar stages of pulmonary tuberculosis in general, indicating a probable better immunity and more stable physiologic equilibrium of the body. In the eighty-one patients with normal sedimentation velocity and manifest pulmonary tuberculosis, the condition was apparently arrested in twenty-six or 32.09 per cent, became quiescent in fourteen or 17.28 per cent, improved in thirty-two or 39.5 per cent and remained unimproved in only six or 7.4 per cent; three or 3.7 per cent died.

The transition from caseation to cavity formation was not rare in this group. Of fifty-four moderately advanced cases, a single cavity was demonstrable in seven and multiple cavities in one. Of thirteen far advanced cases, multiple cavitation was found in two and a single cavity in two. The cavities varied in appearance from honey-combing to spaces from 2 to 4 cm. in diameter. The finding of cavities contributes additional weight to our impression that the use of the sedimentation test for the exclusion of tuberculosis has considerable limitations.

Tuberculous and nontuberculous complications were found among these patients as follows: plastic or exudative pleurisy in six, rectal fistula in three, intestinal tuberculosis in two, tuberculous arthritis in one, mitral stenosis in one, tertiary syphilis in one and diabetes in one.

On the basis of symptoms presented on admission the majority of the patients could not be considered as having benign tuberculosis. Slight cough with expectoration was recorded in thirty-eight, moderate or severe cough with expectoration in thirty-three. The amount of sputum varied from a slight quantity to 120 cc. per day. Cough without expectoration was found in one case, and only in nine cases was the absence of cough and expectoration noted. Almost half of the group complained of pains in the chest. Slight or moderate dyspnea on exertion was seen in forty-four, and marked dyspnea in only four patients. Hemoptysis occurred in thirty-two patients, nine of whom had major pulmonary hemorrhage and two repeated hemoptysis. The temperature taken by mouth during rest periods ranged as high as 40 C. (104 F.) in

which was 7.1, 47 and 45.9 in minimal, moderately advanced and far advanced cases respectively, the percentage in the group that we are analyzing is 17.28, 66.66 and 16.04. These figures show a marked increase in the minimal and moderately advanced cases and a considerable decrease in the far advanced cases. The accompanying table illustrates the frequency of positive sputum, the occurrence of different types of lesions and the presence of cavities in this group.

Positive sputum was found in 21.42 per cent of the cases of minimal, 38.88 per cent of those of moderately advanced and 76.92 per cent of those of far advanced lesions. From this data, it is evident that normal sedimentation velocity and positive sputum may coexist. Since this possibility detracts from the reliability of the sedimentation test in diagnostic work, it should serve as a warning against the enthusiasm of those who consider a normal rate as evidence of the absence of active tuberculosis. A method with such working error should not be considered equal in value to the demonstration of tubercle bacilli in the sputum,

Analysis of Cases of Tuberculosis

Classification	Number	Positive Sputum	Fibrotic	Exudative	Cavity	
					Single	Multiple
Minimal.....	14	3	3	11		
Moderately advanced.....	54	21	6	48	7	1
Far advanced.....	13	10	1	12	2	2
Total.....	81	34	10	71	9	3

or a trustworthy criterion for ruling out tuberculosis, unless all other information—clinical, roentgenographic and laboratory—is corroborative in the same sense. Let us add that in all these patients with positive sputum the bacilli were detected by the simple Ziehl-Neelsen procedure without homogenization.

Another noteworthy observation recorded in this group was that 87.65 per cent of the patients presented an exudative type of lesion on admission and only 12.35 per cent were found to have the fibrotic type of disease. Close analysis of clinical and roentgenographic observations disclosed these data.

To find normal sedimentation velocity in a group of exudative lesions is rather conspicuous and contrary to expectations. Knowing that inflammatory processes are liable to upset the physicochemical balance of the blood, causing a change in the colloidal composition of plasma proteins and an augmentation of the globulins and fibrinogen, one would reasonably suppose an increase in the rate in this type of pulmonary tuberculosis. The exudative process is characterized by typical inflammatory changes that can be visualized as a tuberculous pneumonic patch with a potential tendency to caseation, tissue disintegration and cavity

mentation rate in the great majority of instances. Exceptions to this rule occur. An interesting example was the case of a man, aged 51, admitted to the sanatorium with the characteristic toxic symptoms of tuberculosis, including afternoon chills, fever and night sweats, in whose sputum tubercle bacilli were found; the physical and roentgen examinations revealed typical miliary tuberculosis. The man died three weeks after admission, although his sedimentation rate was 94 per cent, that is, not far from normal. Other examples of extensive exudative lesions with or without cavitation, with positive sputum and marked subjective symptoms and nearly normal sedimentation could be cited; yet we may say that these are the exceptions and not the rule and tend to call attention to these facts: 1. Active tuberculosis usually is accompanied by disturbed colloid balance of the blood, which may be demonstrated by the increased sedimentation rate of the red blood cells. 2. Slight or moderate deviations from the normal rate may have great practical significance and should not be left out of consideration.

It is important to emphasize the fact that not so much the extent of the lesion as the toxicity of the infection is the main factor influencing the sedimentation rate. We observed many patients whose pulmonary involvement was extensive, yet whose sedimentation speed was comparatively slow; on the other hand, we often saw limited lesions with very rapid sedimentation. When toxic symptoms dominate, a rapid sedimentation rate can be expected. Fibrotic processes with less marked symptoms are less liable to show a great difference from normal, whereas virulent infections, with considerable soft infiltration, destruction and cavity formation, are accompanied by an abnormally rapid rate. A very low graph, that is, a very rapid rate, should always be considered an important sign of marked activity, and should serve as a guide in outlining a therapeutic plan for our patients. We have frequently had the opportunity to observe that the sedimentation rate was a more sensitive index of the presence of large amounts of toxins in the body than the temperature or pulse rate. Therefore, it seems desirable that a study of this test be included in the analysis of every case when patients are advised in questions of rest, exercise or further clinical supervision.

No generalized answer can be given to the question of the prognostic value of the sedimentation procedure. Any one familiar with the pathology and nature of tuberculosis, with the variable results of the antagonistic effects of bacterial poisons, decomposed tissue proteins, on one hand, and the body's tendency to resistance, defense and repair, on the other hand, will realize that a single test reflecting a moment's status of the dynamic conflict between body and germs can hardly foretell the outcome of a long series of changes occurring in tuberculosis. Still it may be said with all fair-mindedness that sedimentation velocity slightly

eight patients; in nine patients it reached 38 C. (100.4 F.) or more, and in twenty-two between 37.5 (99.5 F.) and 38 C. The remainder of the patients had temperature ranging from normal to 37.5 C.

Physical observations characteristic of active parenchymal infiltration were recorded in each case, the most frequent being impaired percussion sound, abnormal breath sounds and moist râles. No râles could be heard over the lungs of four patients with minimal and two patients with moderately advanced disease. The diagnosis for these six patients was based on other physical observations, roentgen and laboratory evidence. In the majority of instances the physical and roentgen observations were congruous. Occasionally clinically silent areas were demonstrated by roentgen rays.

In fifty cases of the group in which hematologic studies were made simultaneously with the sedimentation test, secondary anemia was found in twenty-five, the lowest red blood count being 3,570,000 with 50 per cent hemoglobin; the highest leukocyte count encountered was 17,900. Lymphocytosis was frequently seen and the number of cases with a marked increase in the monocyte-lymphocyte ratio was small. Evidently more information could be derived from the blood picture than from the sedimentation rate in this group.

Hilar tuberculosis with a normal sedimentation rate occurred in nineteen children. Normal sedimentation speed was shown in six cases of tuberculous pleurisy and one case of tuberculous peritonitis. Of the fifty-nine orthopedic patients, normal values were found in thirteen. And, finally, eight cases of tuberculous lymphadenitis presented normal sedimentation graphs. These observations suggest that a normal sedimentation rate is not a reliable sign of the absence of extrapulmonary forms of tuberculosis.

Of the 2,000 cases analyzed, normal sedimentation tests were found on admission in 387. This number includes 128 patients with manifest active tuberculosis whose detailed description has been given. The remaining 259 represent cases of upper respiratory catarrh, chronic bronchitis, emphysema, allergic asthma, bronchiectasis, traumatic pulmonary hemorrhage, pneumoconiosis, convalescence from infectious diseases with respiratory complications, exophthalmic goiter, diabetes, chronic osteomyelitis, rickets, postpoliomyelitic scoliosis, tabes, familial optic nerve atrophy, psychoneurosis, chronic pyelitis, myocarditis, malnutrition and no disease; the two latter groups include many contact children who were referred to us for preventorium care.

It can be seen, therefore, that of the 1,741 tuberculous cases, 128 or 7.35 per cent having evidence of active tuberculosis showed normal sedimentation curves. Discounting this shortcoming of the method, we found that the activity of the process has a direct influence on the sedi-

3. The test cannot be used in the diagnosis of tuberculosis unless pathologic conditions causing a similar increase in the sedimentation rate can be excluded.

4. Of the patients having manifest active tuberculosis, 7.35 per cent showed normal sedimentation curves. This group included fourteen cases of minimal, fifty-four of moderately advanced and thirteen of far advanced pulmonary tuberculosis and forty-seven of extrapulmonary tuberculosis.

5. If this working error is discounted, the test gives valuable information concerning the activity of the disease, the amount of tissue destruction and the toxicity of the process. Retarding of the sedimentation speed in a patient in whom it was originally very rapid may be interpreted as a sign of improvement. A constantly increased rate indicates the spread of the disease or the onset of some complication.

6. The test cannot be used for estimating the extent of the lesion. A limited process with marked tissue disintegration and characteristic toxic symptoms will cause a more rapid sedimentation rate than an extensive fibrotic lesion with slight toxicity.

7. A rapid rate found on repeated examinations means an unfavorable prognosis.

8. The greatest merit of the test lies in its value as an index of changes in the general and local condition of the patient. It should be used as a guide for prescribing and controlling routine or special treatment of the tuberculous. It may serve as a valuable aid in connection with the physical examination for determining the patient's working capacity before discharge from the sanatorium and at each reexamination at the dispensary.

or moderately above normal does not have a great significance in this direction. A number of patients who died at the sanatorium presented slightly or moderately higher values than normal on admission. More significance can be attached to a marked increase in speed when it is found repeatedly during the course of the illness. Such results can be considered of grave prognosis.

The greatest merit of this procedure, however, lies in its usefulness in observing the course of the disease, as a sensitive indicator of complications or the development of new foci and as a criterion of results of general routine or any special treatment. Naturally, the prerequisite for obtaining such information is the repetition of the test at regular intervals or from time to time whenever such information is needed, with an accurate standardized technic.

In general, the disappearance of toxic symptoms, the improvement of the patient's physical condition and the decrease in clinical observations are accompanied by a sedimentation rate approaching normal. An increase in toxicity, progress of the disease and a continuously failing physical condition bring an increase in the speed of sedimentation. New foci in the lung tissue are sometimes hidden to diagnostic approach for a considerable length of time, and complications like intestinal or renal tuberculosis are often unsuspected; the increased rate in such cases may direct the attention to the source of disturbance and may enable us to apply appropriate measures. Periodic repetition of this test in cases of pneumothorax, phrenic nerve block and heliotherapy is of extreme value. It not only renders possible the early recognition of complications like pleural effusion or empyema, but, what is even more important, it offers an approximate gage of the extent of improvement when physical or roentgen examination would be of little value. It has been emphasized that minor deviation from normal may indicate gross activity. Therefore, no patient should be classified and discharged as having a quiescent or apparently arrested condition unless his sedimentation rate has returned to normal. It would be advisable to determine the rate of every patient discharged from a sanatorium or under the supervision of a dispensary in connection with each periodic examination.

CONCLUSIONS

1. A study of the sedimentation test in 2,000 patients is reported.
2. Exactly controlled standardized technic and repetition of the test at intervals are essential features of the procedure. Presentation of readings in graphic form and their comparison with the minimal normal graph renders possible an easy visualization of the results. It proved highly practical in our work to record the readings in one figure which represents the percentage of the minimal normal rate.

and Keith,⁸ in 1926, gave ammonium nitrate to animals and to patients and found that patients could tolerate 10 Gm. daily without toxic effects, and that nausea was a much less troublesome symptom than with other ammonium salts. Since then,⁹ we have administered ammonium nitrate in many cases of edema caused by distinctly different pathologic conditions, and usually have obtained satisfactory diuresis without toxic effects. Further experimental work was undertaken to determine the specific effects of nitrates and their site of action. Cahn,¹⁰ in 1886, reported that the concentration of urinary chlorides was increased in the dog after the ingestion of potassium nitrate. Since then it has been frequently confirmed that nitrates produce an increased excretion of chlorides in the urine. The lack of a simple, satisfactory method for the determination of nitrates in body fluids has limited experimental progress in this subject. This difficulty was overcome in the course of the present work by the development of a simple method by one of us (Whelan¹¹). We then proceeded to study the effects, under carefully controlled conditions, of the administration of nitrate on the normal dog, on normal persons and on patients with edema. The present communication gives the results of these studies of the action and excretion of nitrates.

EXPERIMENTS ON THE DOG

Method of Study.—Experiments over short periods of time were carried out on six dogs. Female dogs were used because of the ease of obtaining specimens of urine by catheter. Food or water was not given during the control periods or after intravenous injection of the solution of nitrate. A solution of ammonium nitrate, 10 per cent, was injected intravenously at a maximal rate of 2 cc. (0.2 Gm.) each minute and in the amount of from 0.13 to 0.14 Gm. for each kilogram of body weight. Samples of blood were obtained periodically and the concentration of nitrate nitrogen, ammonia nitrogen and urea nitrogen, and the carbon dioxide combining power of the plasma were determined. At stated intervals, the volume, specific gravity, and hydrogen ion concentration of the urine were measured, and estimations were made of the excretion of nitrate, urea, ammonia nitrogen and chloride.¹² When we were studying the combined effects of nitrate and of organic compounds of mercury, a solution of merbaphen, 10 per cent, was injected intravenously in amounts of from 0.037 to 0.04 cc. for each kilogram of body weight. Results in three of these experiments are given in tables 1, 2 and 3.

8. Jacobs, M. F., and Keith, N. M.: *The Use of Diuretics in Cardiac Edema*, M. Clin. North America **10**:605 (Nov.) 1926.

9. Keith, N. M., and Whelan, Mary: *The Combined Diuretic Action of Certain Acid Producing Salts and Organic Mercury Compounds*, Tr. A. Am. Phys. **41**:181, 1926; Keith, N. M.; Whelan, Mary, and Bannick, E. G.: *The Diuretic Action of Nitrates and Their Use in the Treatment of Dropsy*, Tr. A. Am. Phys. **43**:288, 1928.

10. Cahn, Arnold: *Die Magenverdauung im Chlorhunger*, Ztschr. f. physiol. Chem. **10**:522 (July) 1886.

11. Whelan, Mary: *A Colorimetric Method for the Quantitative Determination of Nitrates and Nitrites in Biologic Fluids*, J. Biol. Chem. **86**:189, 1930.

12. The chloride has been expressed as chlorine and not as sodium chloride.

THE ACTION AND EXCRETION OF NITRATES *

NORMAN M. KEITH, M.D.

MARY WHELAN, M.A.

AND

EDWIN G. BANNICK, M.D.

ROCHESTER, MINN.

Nitrates have long been recognized as effective diuretics. Thomas Willis,¹ in 1679, used potassium nitrate or "the salt of niter" in the treatment of dropsy. Jörg,² in 1825, administered increasing doses of potassium nitrate to a normal man and noted its diuretic effect. Wood,³ in 1856, confirmed the therapeutic action of nitrates, emphasizing the fact that an adequate dose was important in order to produce effective diuresis. Wilks and Taylor,⁴ in 1863, gave as much as 18 Gm. of potassium nitrate a day to a patient with renal dropsy, obtaining satisfactory results. About twenty-five years ago the toxicity of nitrates became a practical problem because of the rather extensive use of bismuth subnitrate in diagnostic roentgen procedures. Cases presenting methemoglobinemia were reported⁵ and consequently the possible toxic action of nitrates was overemphasized, with the resultant use of small and inadequate doses.

Our previous experiments⁶ and those of Gamble⁷ showed that certain ammonium salts, including ammonium chloride and ammonium sulphate, were helpful diuretics. It seemed advantageous to give ammonium nitrate a trial, thus combining the effects of an ammonium salt and the well recognized diuretic action of the nitrate ion. Jacobs

* Submitted for publication, April 15, 1930.

* From the Division of Medicine, the Mayo Clinic, Rochester, Minn.

1. Willis, Thomas: *Pharmaceutics Rationalis*, London, 1674, p. 74.

2. Jörg, J. C. G.: *Materialen zu einer künftigen Heilmittellehre durch versuche der Arzneyen*, Leipzig, Cnoblock, 1825, pp. 500.

3. Wood, G. B.: *A Treatise on Therapeutics and Pharmacology or Materia Medica*, Philadelphia, Lippincott & Company, 1856, vol. 2, p. 595.

4. Wilks, and Taylor, A. S.: *A Large Quantity of Nitrate of Potash Was Taken Medicinally. Elimination of the Salt by the Urine*, *Guy's Hosp. Rep.* 9:173, 1863.

5. Beck, E. G.: *Toxic Effects from Bismuth Subnitrate: With Reports of Cases to Date*, *J. A. M. A.* 52:14 (Jan. 2) 1909.

6. Keith, N. M.; Barrier, C. W., and Whelan, Mary: *Treatment of Nephritis and Edema with Calcium*, *J. A. M. A.* 83:666 (Aug. 30) 1924; Keith, N. M., and Whelan, Mary: *A Study of the Action of Ammonium Chloride and Organic Mercury Compounds*, *J. Clin. Investigation* 3:149 (Oct.) 1926.

7. Gamble, J. L.; Blackfan, K. D., and Hamilton, Bengt: *Study of the Diuretic Action of Acid Producing Salts*, *J. Clin. Investigation* 1:359 (April) 1925.

TABLE 1.—Action of Ammonium Nitrate in the Normal Dog

Date	Time	Blood				Dog 1, Female, Weight 10 Kg.				Dog 2, Female, Weight 12.1 Kg.				Comment	
		Whole Blood		Plasma	Ammonia Nitro-gen, Mg. for Each 100 Cc.	Urea Nitro-gen, Mg. for Each 100 Cc.	Time of Excretion Hours	Minutes	Volume, Cc.	pH	Urea Nitro-gen, Mg. for Each 100 Cc.	Ammonia Nitro-gen, Mg. for Each 100 Cc.	Chloride, Gm. for Each 100 Cc.		
		Ammonia Nitro-gen, Mg. for Each 100 Cc.	Urea Nitro-gen, Mg. for Each 100 Cc.	Carbon Dioxide Combining Power, per Cent											Carbon Dioxide Combining Power, per Cent
7/10/28	10:14 a. m.	0.09	18.7	2	..	10.0	..	3.45	0.07	0.12	No food or water Intravenous injection 13.45 cc. (1.34 Gm.) 10 per cent ammonium nitrate solution begun Intravenous injection finished		
7/11/28	10:18 a. m.			
	10:25 a. m.			
	10:27 a. m.	0.39	18.7	0.5			
	10:37 a. m.	0.10	21.5	19	..	2.0	..	2.23	0.07	0.32	Catheter retained in bladder since 10:14 a. m.; urine excretion in four hours 25.5 cc., a slight increase Urine collected beneath cage Urine collected by catheter		
	10:52 a. m.	0.08	22.9	15	..	2.0	..	1.95	0.32	0.40			
	11:10 a. m.	0.06	18.7	18	..	2.0	..	1.13	0.10	0.46			
	11:25 a. m.	0.06	21.0	15	..	6.5	..	3.06	0.09	0.34			
	12:25 p. m.	18.7	1	..	1.5	..	3.51	0.13	0.14	1000 cc. water; no food Intravenous injection 17.32 cc. (1.73 Gm.) 10 per cent ammonium nitrate begun Intravenous injection finished		
	2:25 p. m.	21.0	2	..	13.0	..	2.15	0.19	0.19			
7/12/28	10:30 a. m.	12.0	20	..	52.0	..	2.72	0.24	0.13			
	23.0			
7/16/28	10:10 a. m.	0.08	14.0	46	..	2	..	19.0	6.4	2.24	0.02	0.15	Intravenous injection 17.32 cc. (1.73 Gm.) 10 per cent ammonium nitrate begun Intravenous injection finished		
7/17/28	10:12 a. m.			
	10:20 a. m.			
	10:21 a. m.	0.25	14.5			
	10:23 a. m.	11	..	16.0	6.4	1.46	0.06	0.31	Catheter retained in bladder since 10:10 a. m.; urine excreted in four hours, ten minutes, 62 cc., a definite increase		
	10:50 a. m.	0.10	16.3	10.0	5.2	1.64	0.09	0.46			
	11:20 a. m.	0.08	14.5	1	..	10.0	5.0	2.23	0.12	0.31			
	12:20 p. m.	19.3	41	1	10.0	5.0	2.23	0.17	0.22			
	2:20 p. m.	14.0	44	2	26.0	5.0	2.33	0.17	0.22			

Action of Ammonium Nitrate in the Normal Dog.—Studies of the blood in these experiments showed that its content of nitrate nitrogen immediately after injection was high, and that this fell gradually in the next eighteen to twenty-four hours. It is of interest to point out this comparatively slow fall of the anion, or nitrate component, compared with the rapid or almost instantaneous disappearance of the chloride ion after ammonium chloride had been administered. The concentration of ammonia nitrogen (table 1) never was very high, but it fell rapidly and reached the normal level in half an hour to one hour after the injection. The concentration of urea nitrogen in the blood was definitely increased in the course of the first two to four hours. This rapid decrease in ammonia and increase in urea of the blood confirms our previous experiences with ammonium chloride.⁶ It indicates that conversion to urea of the ammonia of an ammonium salt occurs soon after the salt enters the blood stream. In a single experiment there occurred a slight fall in the carbon dioxide combining power of the plasma. In further experiments there has been repeatedly a consistent fall of from 10 to 15 per cent by volume.

The volume of urine usually was increased over that of the control period, and in one experiment the amount was actually doubled.¹³ The hydrogen ion concentration and the concentration of chloride increased, as did the concentration of ammonia nitrogen. One of us (Whelan) has obtained similar diuresis and response in excretion of chloride in dogs which were given a solution of nitric acid.¹⁴ The amount of urea nitrogen excreted in the first four hours approximated that excreted during the previous control period in two experiments, but in a third experiment the amount was increased. The nitrate nitrogen was excreted in considerable amounts; from 47 to 57.7 per cent of the amount injected was recovered in the urine in from eighteen to twenty-four hours. The highest concentration reached 0.29 Gm. in each 100 cc. of urine (table 2). These urinary phenomena were similar to those previously observed with ammonium chloride in the dog.⁶ The increase in the volume of urine and content of the chloride was more frequent after the nitrate than after the chloride. It is significant that some nitrates can cause the output of more chloride in the urine than can some chlorides.

Two experiments, one of which is illustrated in table 3, demonstrate how much more effective is the organic compound of mercury, merbaphen, when it is combined with ammonium nitrate. The combined action results in the excretion of approximately twice the amount of water and chloride in a period of twenty hours (fig. 1).

13. The fact that diuresis did not always occur is evidence that the intravenous injection of the small amount of water in which the salt was dissolved did not have a diuretic effect of itself.

14. Whelan, Mary: Unpublished data.

TABLE 3.—Effect of Ammonium Nitrate on Diuresis Caused by Organic Compounds of Mercury (Dog 4, Female, Weight 11.2 Kg.)

Date	Time	Urea Nitro- gen, Mg. for Each 100 Cc. Blood	Time of Excre- tion, Hr.	Urine				Comment
				Vol- ume, Cc.	Specific Gravity	Chloride		
						Gm. for Each 100 Cc.	Gm. Ex- creted	
8/14/28	600 cc. water; no food
8/15/28	10:20 a.m.	17.0	No water or food during experi- ment
	12:20 p.m.	2	7	1.043	0.18	0.01	Urine obtained by catheter at beginning and end of period
	12:24 p.m.	Merbaphen, 0.43 cc., injected intravenously
	2:25 p.m.	16.6	2	10	1.039	0.13	0.01	
	4:25 p.m.	12.0	2	35	1.021	0.71	0.25	
	6:25 p.m.	2	80	1.008	0.59	0.47	
	8:25 p.m.	10.6	2	70	1.007	0.40	0.28	
8/16/28	8:35 a.m.	11.5	12	48	1.020	0.18	0.09	Urine collected beneath cage
				28	1.034	0.08	0.02	Urine collected by catheter, total volume of urine in twenty hours, 271 cc.
9/27/28	600 cc. water; no food
9/28/28	12:17 p.m.	...	2	11	1.023	0.23	0.25	No water or food during experi- ment
	12:19-27 p.m.	1.57 Gm. ammonium nitrate in- jected in 15.75 cc. 10 per cent solution intravenously
	12:30 p.m.	Merbaphen, 0.46 cc., injected intravenously
	2:30 p.m.	2	38	1.019	0.35	0.13	
	4:30 p.m.	2	215	1.008	0.59	1.27	
	6:30 p.m.	2	135	1.010	0.58	0.78	
	8:30 p.m.	2	58	1.011	0.65	0.38	
9/29/28	8:30 a.m.	12	69	1.021	0.15	0.10	Urine collected beneath cage
				13	1.038	0.04	0.005	Urine collected by catheter; total urine volume in twenty hours, 528 cc.

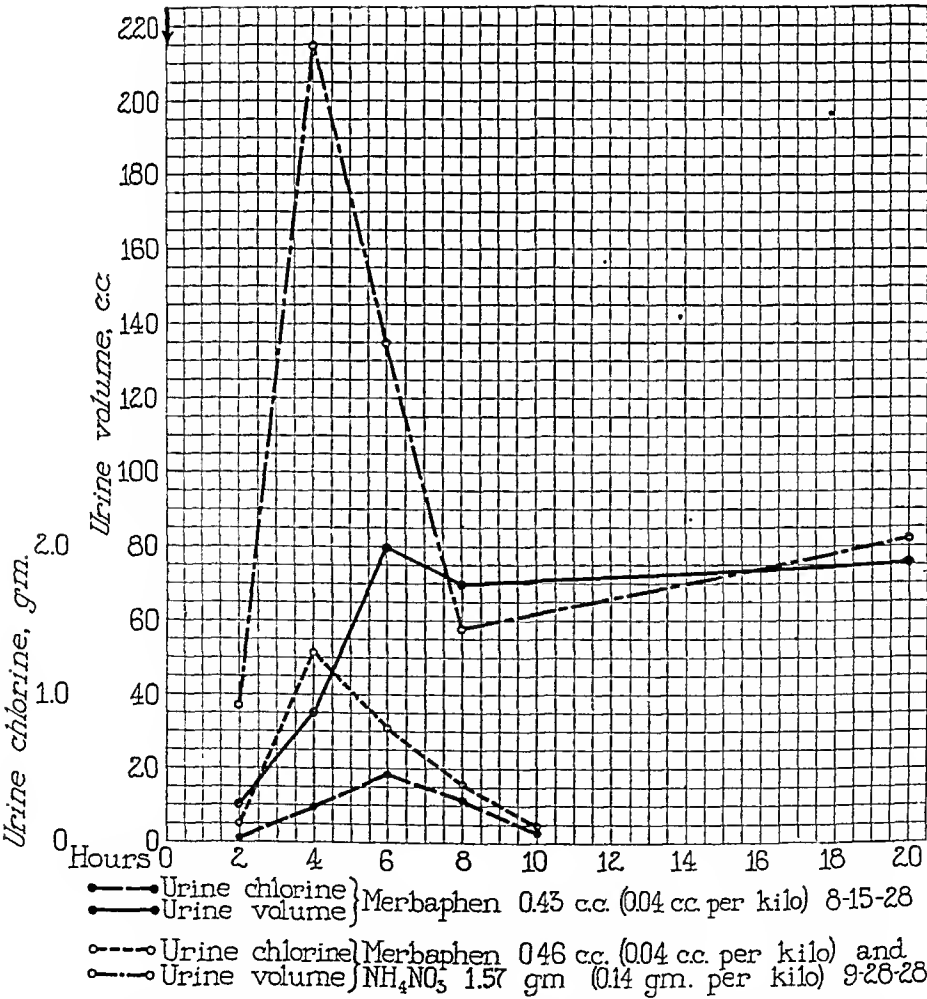


Fig. 1 (dog 4, table 3).—The greater effect of the combined action of merbaphen and ammonium nitrate than merbaphen alone on the renal excretion of water and chloride is shown.

TABLE 2.—Nitrate Excretion in the Dog (Dog 5, Female, Weight 9.44 Kg.)

Date	Time	Nitrate Nitrogen, Mg. for Each 100 Cc. of Plasma	Urine								Comment	
			Nitrate Nitrogen		Chloride		Urea Nitrogen		Ammonia Nitrogen			
			Gm. for Each 100 Cc. Excreted	Gm. Excreted	Gm. for Each 100 Cc. Excreted	Gm. Excreted	Gm. for Each 100 Cc. Excreted	Gm. Excreted	Gm. for Each 100 Cc. Excreted	Gm. Excreted		
10/5/29	8:20 a. m. to		28	trace*	0.23	0.064	2.67	0.75	0.17	0.048	Control six hours
	2:19 p. m.	Intravenous injection 12 cc. 10 per cent solution ammonium nitrate (1.2 Gm. or 0.21 Gm. nitrate nitrogen) begun
	2:21 p. m.	
	2:33 p. m.	.81	Intravenous injection finished
	3:05 p. m.	5.7	
	3:37 p. m.	4.9	
10/6/29	4:35 p. m.	4.0	
	6:35 p. m.	1.9	Volume, chloride, urea and ammonia output equal to that of control period
	8:35 p. m.	1.2	28	0.291	0.081	0.28	0.078	2.56	0.72	0.20	0.056	
	2:35 a. m.	0.65	13	0.105	0.014	0.12	0.016	2.68	0.35	0.30	0.039	Total nitrate nitrogen excreted in eighteen hours, 0.099 Gm. (47 per cent of amount injected); no food or water given during experiment
	8:35 a. m.	0.52	13	0.030	0.004	0.02	0.003	2.96	0.38	0.42	0.054	

* Very small amount; difficult to estimate.

In determining nonprotein nitrogen, the methods of Folin and Denis¹⁸ were employed. Urea nitrogen was determined by van Slyke and Cullen's¹⁹ modification of Marshall's method, and ammonia nitrogen by the method of Nash and Benedict.²⁰ Cholesterol was determined by the method of Bloor and Knudson;²¹ creatinine by the method of Folin and Wu;²² proteins of the serum or plasma by the method of Howe,²³ and plasma chlorides were determined according to the technic of Osterberg and Schmidt²⁴ with slight modifications; the technic is the same except that 9 cc. of the dilute nitric acid is added to 1 cc. of serum or plasma followed by 2 cc. of silver nitrate (1 cc. of which is equivalent to 4 mg. of sodium chloride) and centrifugated. An aliquot part or 10 cc. of this is titrated with ammonium thiocyanate. The determination of base was carried out according to the method of Stadie and Ross.²⁵ Bicarbonate was determined by the method of van Slyke and Cullen,²⁶ and of van Slyke and Stadie.²⁷ The nitrate nitrogen was estimated by the method of Whelan.¹¹ The carbon dioxide combining power of the serum was determined by the procedure of van Slyke and Cullen.²⁶ Calcium was determined by the method of Clark and Collip²⁸ which is a modification of the method of Kramer and Tisdall.²⁹ The method of Kramer and Tisdall²⁹ was used for precipitation of the magnesium as magnesium ammonium phosphate. The phosphorus in the precipitate was determined by the method of Fiske and Subbarow.³⁰ Sulphates were determined by a method

18. Folin, Otto, and Denis, W.: Non-Protein Nitrogen in Blood, *J. Biol. Chem.* **26**:491, 1916.

19. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, *J. Biol. Chem.* **19**:211, 1914.

20. Nash, T. P., Jr., and Benedict, S. R.: Ammonia Content of the Blood and Its Bearing on the Mechanism of Acid Neutralization in the Animal Organism, *J. Biol. Chem.* **68**:463 (Oct.) 1921.

21. Bloor, W. R., and Knudson, Arthur: Cholesterol and Cholesterol Esters in Human Blood, *J. Biol. Chem.* **29**:7, 1917.

22. Folin, Otto, and Wu, Hsien: A System of Blood Analysis, *J. Biol. Chem.* **38**:81 (May) 1919.

23. Howe, P. E.: The Determination of Proteins in Blood, a Micro Method, *J. Biol. Chem.* **49**:109 (Nov.) 1921.

24. Osterberg, A. E., and Schmidt, Edna V.: Estimation of Plasma Chlorides, *J. Lab. & Clin. Med.* **13**:172 (Nov.) 1927.

25. Stadie, W. C., and Ross, Effie C.: A Micro Method for the Determination of Base in Blood and Serum and Other Biological Materials, *J. Biol. Chem.* **65**:735 (Oct.) 1925.

26. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: 1. The Bicarbonate Concentration of the Blood Plasma, Its Significance and Its Determination as a Measure of Acidosis, *J. Biol. Chem.* **30**:289, 1917.

27. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, *J. Biol. Chem.* **49**:1 (Nov.) 1921.

28. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J. Biol. Chem.* **63**:461 (March) 1925.

29. Kramer, Benjamin, and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, *J. Biol. Chem.* **47**:475 (Aug.) 1921.

30. Fiske, C. H., and Subbarow, Yellapragada: The Colorimetric Determination of Phosphorus, *J. Biol. Chem.* **66**:375 (Dec.) 1925.

EXPERIMENTS ON NORMAL MEN

Method of Study.—Detailed metabolic studies both before and after the ingestion of nitrates were carried out on four normal young men. In order to have accurate experimental conditions, these subjects were given a constant weighed diet, low in content of mineral salts and of water, but adequate in protein and total calories. Except for variation in vegetables, the same food was given each day. A carefully made record was kept of any food not eaten. In table 4 are given the calculated values of certain of the constituents and the variations of the diet. The additional daily intake of water was measured; it amounted to between 200 and 800 cc., usually from 600 to 800 cc. Daily specimens of urine were collected, and in some cases, daily collections of stools were made also. There was always a preliminary control period of from two to four days, so that the storage of water and salts was at a minimum. The subjects were then given from 8 to 10 Gm. of ammonium nitrate daily, in single or divided doses, over varying periods of time. The ammonium nitrate was given in 25 or 30 per cent solution flavored with peppermint water. To normal man 3, sodium nitrate and ammonium acetate were also administered in solution under conditions similar to those under which ammonium nitrate was given, and in amounts approximately equivalent to those in which ammonium nitrate was given.

TABLE 4.—*Composition of Low Mineral and Low Water Diets in Grams*

Type	Car- bohy- drates	Pro- tein	Fat	Calo- ries	Water	Sod- ium	Po- tas- sium	Cal- cium	Mag- ne- sium	Chlo- ride	Phos- phorus	Sul- phur	Iron
1	175	50	126	2,095	872	0.75	1.77	0.29	0.21	0.87	0.74	0.69	0.011
2	230	59	93	2,050	890	0.70	2.29	0.35	0.21	0.86	0.87	0.80	0.013
3	240	50	144	2,530	895	0.77	1.87	0.31	0.22	0.89	0.75	0.70	0.011
4	300	60	110	2,500	895	0.70	2.21	0.27	0.22	0.87	0.87	0.80	0.013

We have considered the quantitative development of color with the diphenylbenzidine reagent in the urine and body fluids after the ingestion of nitrates as being due to nitrates. It could be due to nitrites, as has been pointed out by one of us (Whelan), but if such large amounts had been present, as would be indicated by the changes in color that have taken place, very toxic symptoms would have developed. Further chemical studies are being carried out in order to estimate separately the concentration of nitrate and nitrite in a given body fluid.¹⁵

In these subjects, samples of blood were taken periodically before breakfast. The concentration in the whole blood of various constituents was determined. Haden's method¹⁶ for the determination of hemoglobin was used, except that the color was developed according to the method devised by Osgood and Haskins.¹⁷

15. Several substances that are normally present and others that might possibly be found in body fluids in these subjects and in cases of edema were tested with the nitrate reagent. The color reaction did not develop with solutions of the following substances: dextrose, skatol, glycuronic acid (borenol glycuronic acid), diabetic urine, phenobarbital, acetylsalicylic acid, theophylline-ethylenediamine and the organic mercury compounds, merbaphen and mersalyl (salyrgan).

16. Haden, Russell: A Method for the Determination of Hemoglobin, *J. Lab. & Clin. Med.* 8:411 (March) 1923.

17. Osgood, E. E., and Haskins, H. D.: A Permanent Standard for the Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* 57:107 (Aug.) 1923.

Kjeldahl digestion. Thus, we were able to carry out separate estimations of the usual nitrogenous constituents of the urine and stool, and of the nitrates. In consequence, it is possible to distinguish between changes in metabolism of nitrate and the effects of the nitrate on the general metabolism of the body, especially that of protein and of nitrogen. In the present study, the term nitrogen balance is used in the latter sense.⁴⁰

ACTION OF AMMONIUM NITRATE AND OF SODIUM NITRATE

Studies of the blood of normal persons showed that the concentration of nitrate nitrogen of the plasma rose to between 2 and 3 mg. in each 100 cc., during the administration of the nitrate, but that after its withdrawal, the concentration fell rapidly in forty-eight hours. In a single experiment the ammonia nitrogen rose slightly to 0.16 mg. in each 100 cc., confirming the rapid disappearance observed in the dog. There were no marked or constant shifts in the concentration of hemoglobin. The concentration of urea nitrogen usually did not change, but in one experiment it rose slightly, as did the total nonprotein nitrogen. The concentration of the nonprotein nitrogen decreased in two instances. The concentration of chloride in the plasma did not vary consistently, nor was there consistent change in the carbon dioxide combining power. The latter phenomenon was in distinct contrast to the fall in carbon dioxide combining power seen after the ingestion of similar amounts of ammonium chloride, as noted by Haldane,⁴¹ Keith, Barrier and Whelan,⁶ Gamble, Blackfan and Hamilton⁷ and Folling.⁴²

The effects of ammonium nitrate on urinary excretion were surprisingly similar in the first three normal subjects represented in tables 5, 6 and 7. The increase in volume of the urine, hydrogen ion concentration, concentration of chloride, total fixed base, nitrate nitrogen, total nitrogen, urea nitrogen and ammonia nitrogen were definite and sometimes marked. There was frequently a small increase in inorganic sulphates, inorganic phosphates and titratable acidity. It is evident that the increased excretion of certain of these substances was due to the ingested nitrate because of the marked decrease in output during the second control period. During the second control period the volume of urine and the concentration of many of the urinary constituents were actually less than during the initial control days. This indicates that the tissues had been deprived of these substances and of water in considerable amounts and tended to retain what remained. This was particularly noticeable in regard to water, chloride and total fixed base (table 5).

40. The total nitrogen balance, including the nitrate, can be calculated readily from the tables.

41. Haldane, J. B. S.: Experiments on the Regulation of the Blood's Alkalinity, *J. Physiol.* **55**:265 (Aug.) 1921.

42. Folling, A.: On the Mechanism of the Ammonium Chloride Acidosis, *Acta med. Scandinav.* **71**:221, 1929.

devised by Wakefield and Power.³¹ The protein content of serum was estimated from its content of nitrogen as determined by the Kjeldahl method. The content of water was determined by drying a known amount of serum to a constant weight. Potassium and sodium were determined by the methods of Kramer and Tisdall,³² except that certain modifications of their method for determination of sodium were made.

The specific gravity of the urine was recorded and the hydrogen ion concentration was determined by the method of Gillespie.³³ The total acidity was determined by the method of Folin.³⁴ Other constituents studied were as follows: the chloride in the urine that did not contain protein by the method of Volhard and Harvey;³⁵ the chloride in the urine that contained protein by Wilson and Ball's method³⁶ for blood chlorides, the phosphorus by the method of Fiske and Subbarow,³⁰ and the sulphate by the method of Folin.³⁷ When protein nitrogen was present in the urine (as in the cases of edema that are to be presented) it was determined by getting the difference between the total nitrogen and the non-protein nitrogen. The method of Folin and Denis³⁸ was used. The protein was precipitated by acid tungstate. Urea nitrogen was estimated by the same method used in estimating it in the blood. Creatinine nitrogen was determined by the method of Folin.³⁹ Ammonium nitrogen was determined by the usual aeration method. Nitrate nitrogen was determined by the method devised by Whelan¹¹ not only in the blood and the urine but also in saliva and edema fluid.

In normal man 4, a study was made of the combined action of nitrate and the organic compound of mercury, mersalyl. A 10 per cent solution of this substance was injected intravenously in doses of 1 cc. The total amount of nitrogen in the stools was determined by the Kjeldahl method in the cases in which studies of nitrogen balance were carried out. In certain persons, the amount of nitrate nitrogen in the stools also was determined by the modified Divarda method, since our colorimetric method was unsatisfactory when it was applied to the specimens of stool. In order to determine the nitrogen balance in persons who were taking nitrate, it was necessary to estimate the concentration of nitrate nitrogen in the urine and feces, since nitrates are broken down and pass off during the usual

31. Wakefield, E. G., and Power, M. H.: A New Iodometric Method for the Quantitative Determination of Inorganic Sulphates in Blood Serum, *J. Biol. Chem.*, in press.

32. Kramer, Benjamin, and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Potassium in Small Amounts of Serum, *J. Biol. Chem.* **46**:339 (April) 1921; A Simple Method for the Direct Quantitative Determination of Sodium in Small Amounts of Serum, *J. Biol. Chem.* **46**:467 (May) 1921.

33. Gillespie, L. J.: Colorimetric Determination of Titration Curves Without Buffer Mixture, *J. Am. Chem. Soc.* **42**:742 (April) 1920.

34. Folin, Otto: Acidity of the Urine, *Am. J. Physiol.* **9**:265 (July) 1903.

35. Harvey, S. C.: The Quantitative Determination of the Chlorides in Urine, *Arch. Int. Med.* **6**:12 (July) 1910.

36. Wilson, D. W., and Ball, E. G.: A Study of the Estimation of Chlorides in Blood and Serum, *J. Biol. Chem.* **79**:221 (Sept.) 1928.

37. Folin, Otto: On Sulphate and Sulphur Determinations, *J. Biol. Chem.* **1**:131, 1905.

38. Folin, Otto, and Denis, W.: Nitrogen Determinations by Direct Nesslerization. Total Nitrogen in Urine, *J. Biol. Chem.* **26**:473 (Sept.) 1916.

39. Folin, Otto: On the Determination of Creatinine and Creatine in Urine, *J. Biol. Chem.* **17**:469, 1914.

TABLE 6.—Nitrogen Metabolism (Normal Man 3)

Date, 1928	Body Weight, kg.	Nitrogen Intake		Blood*			Urine				Feces and Urine, Total Nitro- gen, Gm.	Feces, Total Nitro- gen, Gm.	Comment	
		Total, Gm.	Food, Gm.	Am- monia, Gm.	Non- protein Nitro- gen, 100 Cc.	Urea Nitro- gen, 100 Cc.	Nitrate Nitro- gen, 100 Cc.	Total Non- protein Nitro- gen, Gm.	Urea Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.				Creat- inine Nitro- gen, Gm.
2/18	77.3		
2/18-19	76.7	9.6	9.6	10.35	6.95	0.51	0.67	0.51	10.86	
2/19-20	76.4	9.6	9.6	11.20	7.50	0.36	0.63	11.20	
2/20-21	76.0	9.6	9.6	12.90	9.50	0.48	0.69	2.13	15.03	
2/21-22	75.8	9.6	9.6	35	15	0.06	9.90	7.55	0.33	0.73	9.90	Nitrogen balance (4 days), daily average -2.1 Gm.
2/22-23	75.8	11.35	9.6	1.75	11.00	8.70	0.74	0.68	2.34	13.34	10 Gm. ammonium nitrate given
2/23-24	74.8	11.35	9.6	1.75	9.90	9.70	1.11	0.78	11.20	10 Gm. ammonium nitrate given
2/24-25	74.3	11.35	9.6	1.75	14.7	11.25	1.31	0.84	2.95	17.65	10 Gm. ammonium nitrate given
2/25-26	74.3	11.35	9.6	1.75	2.8	12.8	9.70	1.47	0.78	12.80	10 Gm. ammonium nitrate given, total 40 Gm.; nitrogen balance (4 days), daily average -0.6 Gm.
2/26-27	74.8	9.6	9.6	30	15	3.1	8.7	6.56	1.26	0.75	1.85	10.55	
2/27-28	75.0	9.6	9.6	1.2	8.6	6.95	0.75	0.65	8.60	
2/28-3/1	75.1	9.6	9.6	0.2	8.6	7.45	0.73	0.70	8.60	
3/ 1-2	75.1	9.6	9.6	0.01	9.7	8.54	0.69	0.74	2.20	11.90	Nitrogen balance (4 days), daily average -0.3 Gm.

* Blood taken and body weight determined before breakfast at end of twenty-four hour period.

† Given in 25 per cent solution; diet 4, additional daily water 800 cc.

TABLE 5.—Daily Average of Urine and Total Nitrogen Balance

	Age, Years	Sex	Body Weight, Kg.	Volume of Urine, Cc.	pH	Chloride, Gm.	Total Fixed Base, Cc. of 0.1 Normal	Non- protein Nitrogen, Gm.	Protein Nitro- gen, Gm.	Urea Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Great- ly in- creased, Gm.	Nitrogen Balance, Gm.	Nitrate Nitrogen Balance, Gm.
Normal man 1.	30	M	57.7	850	6.0	0.80	998	8.24	6.38	0.39
First control period.	56.3	1,030	5.6	1.19	1,375	10.39	8.00	0.93
Nitrate period*	56.8	785	6.2	0.16	248	8.67	6.56	0.78
Second control period.
Normal man 2.	34	M	72.6	695	5.5	0.69	541	7.32	5.76	0.67	0.48	-0.1
First control period.	69.9	990	4.9	1.43	1,043	9.38	7.28	1.37	0.51	-0.1
Nitrate period	69.2	580	5.4	0.12	284	7.51	6.64	0.52	0.46	-0.1
Second control period.
Normal man 3.	28	M	75.8	810	6.2	1.19	1,007	11.09	7.88	0.42	0.68	-2.1
First control period.	74.3	1,000	5.4	1.44	1,399	12.4	9.84	1.15	0.77	-0.6	+0.36
Nitrate period	75.1	520	5.9	0.33	414	8.9	7.37	0.86	0.70	-0.3	-0.14
Second control period.
Normal man 3 (sodium nitrate)
First control period.	75.3	810	6.0	1.34	1,036	9.10	7.52	0.39	0.69	0	+0.41
Nitrate period	74.6	895	5.8	1.12	1,657	8.96	7.41	0.30	0.73	-0.6	+0.35
Second control period.	74.6	750	6.2	0.38	690	6.00	4.52	0.21	0.48
Normal man 3 (ammonium acetate)
First control period.	77.0	680	5.8	1.53	1,090	8.75	6.59	0.26	0.73	+0.1
Nitrate period	76.1	475	5.6	0.33	710	10.66	8.96	0.41	0.74	-0.2
Second control period.	76.0	475	5.6	0.33	640	10.50	8.93	0.42	0.74
Chronic glomerulonephritis with edema (case 1)	40	F
First control period.	62.9	745	6.2	0.98	..	5.53	1.58	3.65	0.56	0.40	0
Nitrate period	61.8	1,330	5.2	2.49	..	5.14	1.15	3.65	0.62	0.43	+2.0
Second control period.	60.0	1,060	6.6	0.98	..	4.24	1.18	3.05	0.37	0.38	+0.8
Chronic glomerulonephritis with edema (case 2)	30	M
First control period.	94.1	525	6.2	1.53	996	6.11	2.66	4.85	0.34	0.57	-2.0
Nitrate period	87.8	745	5.9	2.03	1,277	5.99	2.32	4.51	0.57	0.54	-1.2
Second control period.	78.0	1,130	6.8	4.75	2,221	5.64	2.83	4.20	0.42	0.51	-2.2
Chronic nephrosis (case 3)	15	F
Control period	57.3	875	3.08	0.62	+3.3
Nitrate period	53.5	1,250	5.93	1.24	+0.38
Chronic glomerulonephritis with edema (case 4)	24	F
Control period	78.6	1,325	5.6	2.72	1,590	3.80	2.93	2.31	0.32	0.27	+2.1
Nitrate period	74.5	1,840	5.3	4.66	2,219	5.47	3.30	3.74	0.31	0.265	+1.9	+1.02
Chronic nephrosis (case 5)	24	M
First control period.	72.7	595	5.6	0.52	590	9.30	1.91	8.02	0.36	0.59	-2.9	+0.43
Nitrate period	69.1	935	5.5	2.97	1,386	10.90	1.09	9.07	0.65	0.52	-2.0
Second control period.	70.0	595	5.7	0.31	292	8.64	0.91	6.77	0.95	0.50	-1.6	-0.28
Chronic nephrosis (case 6)	47	M
Control period	72.6	600	5.8	2.09
Nitrate period	66.4	1,105	5.4	3.07
Second control period.	65.8	550	5.4	1.60

* Ammonium nitrate given unless otherwise stated.

The excretion of nitrate was determined in normal man 3 (table 7) after the ingestion of ammonium nitrate. The concentration of nitrate nitrogen in the urine varied from 0.01 to 0.15 Gm. in each 100 cc. Seventy-nine per cent of the nitrate ingested was excreted during the period of intake, whereas up to 88 per cent was recovered if the concentration of nitrate in the urine was estimated during the subsequent three to four days. The curve of excretion and the total amount eliminated were essentially the same whether the drug was given as ammonium nitrate or as sodium nitrate (tables 8 and 9 and fig. 2).

The increased excretion of total nitrogen after ammonium nitrate had been given was accompanied by increases in inorganic sulphate and in the urea and ammonia and in one experiment (normal man 3, table 6) in the creatinine fraction. The ratio of inorganic sulphate to total nitrogen in the urine tends to be constant. The excretion of urea nitrogen increased from 1.5 to 2.3 Gm. a day and the total nitrogen from 1.3 to 2.1 Gm. in the different experiments. This increase in urea can be wholly explained by the conversion of the ingested ammonia of the ammonium nitrate to urea. Liberation of urea from the tissues, due to changes in metabolism of water and of minerals, is also a possible source of this increase in the excretion of nitrogen and of urea, but the experiments on nitrogen balance suggest that if the increase is due to these changes, it is of less significance. The increase in ammonia nitrogen appears to be a part of the attempt of the tissues to neutralize the action of the nitrate anion. This increase in ammonia often is prolonged after the ingestion of nitrate has been discontinued, an observation noted by Folling after administration of ammonium chloride. This fact suggests that when retention of salts, including chloride and fixed base, takes place, ammonia remains the chief factor in neutralization and continues to be excreted.

Experiments on nitrogen balance have been carried out in animals by Grafe,⁴³ Grafe and Wintz,⁴⁴ and Abderhalden and Hirsch,⁴⁵ and sodium nitrate has been shown to cause retention of nitrogen, even when the nitrate is quantitatively excreted. It should be stated that the methods for quantitative estimation of nitrate used in their experiments were not found to be accurate in our hands. Grafe and Wintz also

43. Grafe, E.: Zur Frage der Eiweissynthese bei Fütterung von Ammoniaksalzen, *Verhandl. d. Kong. f. inn. Med.* **29**:507, 1912.

44. Grafe, E., and Wintz, H.: Ueber die Beeinflussung des Stickstoff-Stoffwechsels durch Fütterung von Natriumnitrat, *Ztschr. f. physiol. Chem.* **86**:283 (July) 1913.

45. Abderhalden, Emil; and Hirsch, Paul: Weiterer Beitrag zur Kenntnis der synthetischen Fähigkeiten der tierischen Zelle. Die Wirkung des Salpeters (Natrium-nitrats) auf den Stickstoffstoffwechsel, *Ztschr. f. physiol. Chem.* **84**: 189 (April) 1913.

TABLE 7.—*Mineral Metabolism (Normal Man 3)*

Date, 1928	Blood*										Urine										Comment		
	Plasma					Nitrate Carbon					Sulphate as					Nitrate							
	Hemo- Chloro- Nitrate					Phosphorus					Chloride					Nitrogen							
	Nitro- globin, ride, gen, Com- bling					Nitro- Nitro- Dioxide					Chloride					Nitrogen							
	Intake, 100 Ce.	Each 100 Ce.	for 100 Ce.	Each 100 Ce.	Vol- ume, Ce.	pn	Gm.	N/10	Ce.	Gm.	N/10	Ce.	Gm.	N/10	Ce.	Gm.	N/10	Ce.	Gm.	N/10		Ce.	Gm.
2/18-19	900	6.2	2.16	310	0.51	106	1.46	365	0.001	1.3	...	222	1,119	0.51	360				
2/19-20	850	5.8	1.62	455	0.63	204	1.47	368	0.003	1.9	...	278	976	0.36	262				
2/20-21	850	6.4	1.19	336	0.77	249	1.56	390	0.002	1.2	...	204	1,040	0.48	340				
2/21-22	...	17	345	0.06	58	5.8	0.78	210	0.60	194	1.53	383	0.000	0.3	...	192	794	0.33	245				
2/22-23	1.75	825	5.6	1.49	420	0.69	224	1.36	340	1.01	722	+0.64	279	1,340	0.74	525				
2/23-24	1.75	950	5.4	1.61	455	0.84	270	1.62	405	1.48	1,055	+0.27	274	1,567	1.11	793				
2/24-25	1.75	2.8	1,175	5.2	1.53	430	1.04	334	1.80	450	1.42	1,015	+0.33	330	1,540	1.31	935				
2/25-26	1.75	17.8	405	3.1	56	5.2	1.15	324	0.93	298	1.78	445	1.65	1,180	+0.10	252	1,150	1.47	1,050				
2/26-27	385	1.2	450	5.8	0.54	152	0.78	250	1.49	373	0.37	262	-0.37	198	460	1.26	900				
2/27-28	0.2	650	6.0	0.31	88	0.53	170	1.40	350	0.16	116	-0.16	161	399	0.76	543				
2/28-3/1	0.01	425	5.8	0.21	59	0.61	196	1.58	395	0.04	31	-0.04	174	348	0.73	520				
3/1-2	550	6.0	0.26	73	0.62	193	1.47	366	0.006	4.3	-0.01	185	450	0.69	493				

* Blood taken at end of twenty-four hour period.

† Given in 25 per cent solution; diet 4, additional daily water 800 cc.

TABLE 9.—*Mineral Metabolism (Normal Man 3)*

Date, 1923	Blood			Urine										Comment										
	Nitrate Gm.	Hemo- globin, Gm.	Carbon Dioxide Com- bining Capacity, Gm. per Cent by Volume	Chloride					Phosphorus		Sulphate as Sulphur Trioxide		Nitrate		Nitro- gen Bal- ance, Gm.	Titra- table Acid- ity, Cc.	Total Fixed Base, Cc.	Ammonia Nitrogen						
				Vol- ume, Cc.	pH	Gm.	N/10	Cc.	Gm.	N/10	Cc.	Gm.	N/10					Cc.	Gm.	N/10	Cc.	Gm.	N/10	Cc.
3/18-19	775	6.8	2.32	654	0.57	187	1.15	238	121	1,255	0.33	233							
3/19-20	900	6.2	1.26	255	0.70	226	1.52	380	245	1,040	0.42	302							
3/20-21	875	6.2	0.88	248	0.98	316	1.61	402	235	930	0.37	263							
3/21-22	15.7	382	74	700	6.0	0.91	256	206	1.46	365	135	820	0.43	307							
3/22-23	1.65	700	5.8	0.98	276	0.73	234	1.43	358	0.97	683	224	1,325	0.39	280	10 Gm. sodium nitrate given*						
3/23-24	1.65	1,100	6.0	1.65	465	0.65	210	1.39	348	1.39	994	158	1,970	0.22	157	10 Gm. sodium nitrate given						
3/24-25	1.65	15.6	400	900	5.8	0.81	228	0.69	221	1.48	370	1.29	925	195	1,680	0.25	180	10 Gm. sodium nitrate given						
3/25-26	1.65	15.6	..	875	6.2	1.05	296	0.69	221	1.52	381	1.31	937	144	1,655	0.32	231	10 Gm. sodium nitrate given						
3/26-27	364	750	6.4	0.88	108	0.42	136	0.83	208	0.35	250	86	690	0.21	150	given, total 40 Gm.						

* Given in 25 per cent solution; diet 4, additional daily water 800 cc.

TABLE 8.—Nitrogen Metabolism (Normal Man 3)

Date, 1928	Body Weight, Kg.	Nitrogen Intake		Blood*			Urine					Feces and Urine, Total Nitro- gen, Gm.	Comment	
		Total, Gm.	Food, Gm.	Non- protein Nitrogen, Mg. for Each 100 Cc.	Urea Nitro- gen, Mg. for Each 100 Cc.	Nitrate Nitro- gen, Mg. for Each 100 Cc.	Vol- ume, Cc.	Total Non- protein Nitro- gen, Gm.	Urea Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inine Nitro- gen, Gm.			Feces, Total Nitro- gen, Gm.
3/18	76.1	
3/18-19	75.7	...	9.6	775	6.70	5.52	0.33	0.62	...	6.70	
3/19-20	75.3	...	9.6	900	9.50	7.82	0.42	0.68	2.53	12.03	
3/20-21	75.3	...	9.6	875	10.50	8.70	0.37	0.77	...	10.50	
3/21-22	75.3	...	9.6	33	12.6	Trace	700	9.80	8.05	0.43	0.71	...	9.80	Nitrogen balance (four days) 0
3/22-23	75.1	9.6	9.6	2.08	700	8.95	7.35	0.39	0.71	2.45	11.40	10 Gm. sodium nitrate given†
3/23-24	74.6	9.6	9.6	1.88	1,100	9.90	8.05	0.22	0.75	...	9.90	10 Gm. sodium nitrate given
3/24-25	74.6	9.6	9.6	...	12.6	2.44	900	8.69	7.13	0.25	0.73	...	8.60	10 Gm. sodium nitrate given
3/25-26	74.6	9.6	9.6	31.4	12.2	2.64	875	8.40	7.10	0.32	0.73	2.34	10.74	10 Gm. sodium nitrate given, total 40 Gm., nitrogen balance (4 days), daily average —0.6 Gm.
3/26-27	74.6	9.6	9.6	1.06	750	6.00	4.52	0.21	0.49	...	6.35	

* Specimen of the blood taken and body weight determined before breakfast at end of twenty-four hour period.

† Given in 25 per cent solution; diet 4, additional daily water 800 cc.

was definitely less marked than that of ammonium nitrate (tables 8 and 9). The hydrogen ion concentration of the urine and the excretion of ammonia were not increased, which is evidence that there was not a marked disturbance in the acid-base equilibrium. The increase in nitrate and chloride had been met by excess excretion of a fixed base, the source of which most probably was the sodium of the ingested sodium nitrate. The observations in one experiment (tables 10 and 11), after the ingestion of ammonium acetate, are significant. This salt was purposely given to ascertain the effect of the ammonium radical, for the acetate portion of the salt is known to be readily catabolized and rapidly excreted as carbon dioxide and water, the former by way of the lungs, and thus has no appreciable effect on the acid-base equilibrium. This substance had no effect on the hydrogen ion concentration or on the excretion of inorganic salts or water; the latter actually decreased as the experiment progressed. This decrease in the excretion of water and inorganic salts was to be expected because of the very low content of water and salts in the diet. As was anticipated, there was an increased excretion of total nitrogen and urea. The actual increase in ammonia nitrogen was slight. The considerable rise in the concentration of blood urea nitrogen, from 15 to 22 mg. in each 100 cc., probably was partially related to the small output of water in the urine. We reported a like result in a normal man after he had taken ammonium chloride. These results with ammonium acetate suggest that the more marked diuretic effect from ammonium nitrate is not due to the ammonium radical, but to a specific effect of the nitrate. The greater activity of ammonium nitrate, in contrast to sodium nitrate, depends on the difference in the character of the base with which the nitrate ion is combined. The decrease in body weight, especially after administration of ammonium nitrate, appears to be due to the loss of water.

In normal man 4, diuresis occurred on the first day of the control period; that is just after the diet low in salt was instituted. The volume of urine on that day was 2,150 cc., and the excretion of chloride 5.38 Gm. Nonnenbruch⁴⁶ has shown that a diet low in salt, similar to that used in this experiment, may cause diuresis in the normal subject. After this diuresis had subsided mersalyl was given, both before and after the ingestion of ammonium nitrate. During the entire experiment, routine examinations of the urine did not reveal any albumin or abnormality in the sediment. The measurable diuretic effect of the two administrations of this drug was approximately the same. However, at the time of the second injection, the store of water and inorganic salts had

46: Nonnenbruch, W.: Ueber Diurese, *Ergebn. d. inn. Med. u. Kinderh.* **26**: 119, 1924.

found that ammonium salts, although they did not include nitrate, gave rise to retention of nitrogen. In the present study, the nitrogen balance was calculated in four experiments, once in normal man 2, and on three occasions in normal man 3 (table 5). Normal man 2 was in nitrogen equilibrium throughout. In the first experiment on normal man 3, during the initial control period, the man was in negative balance. When he was taking ammonium nitrate, the previous negative balance was decreased, and in the second control period this decrease was even

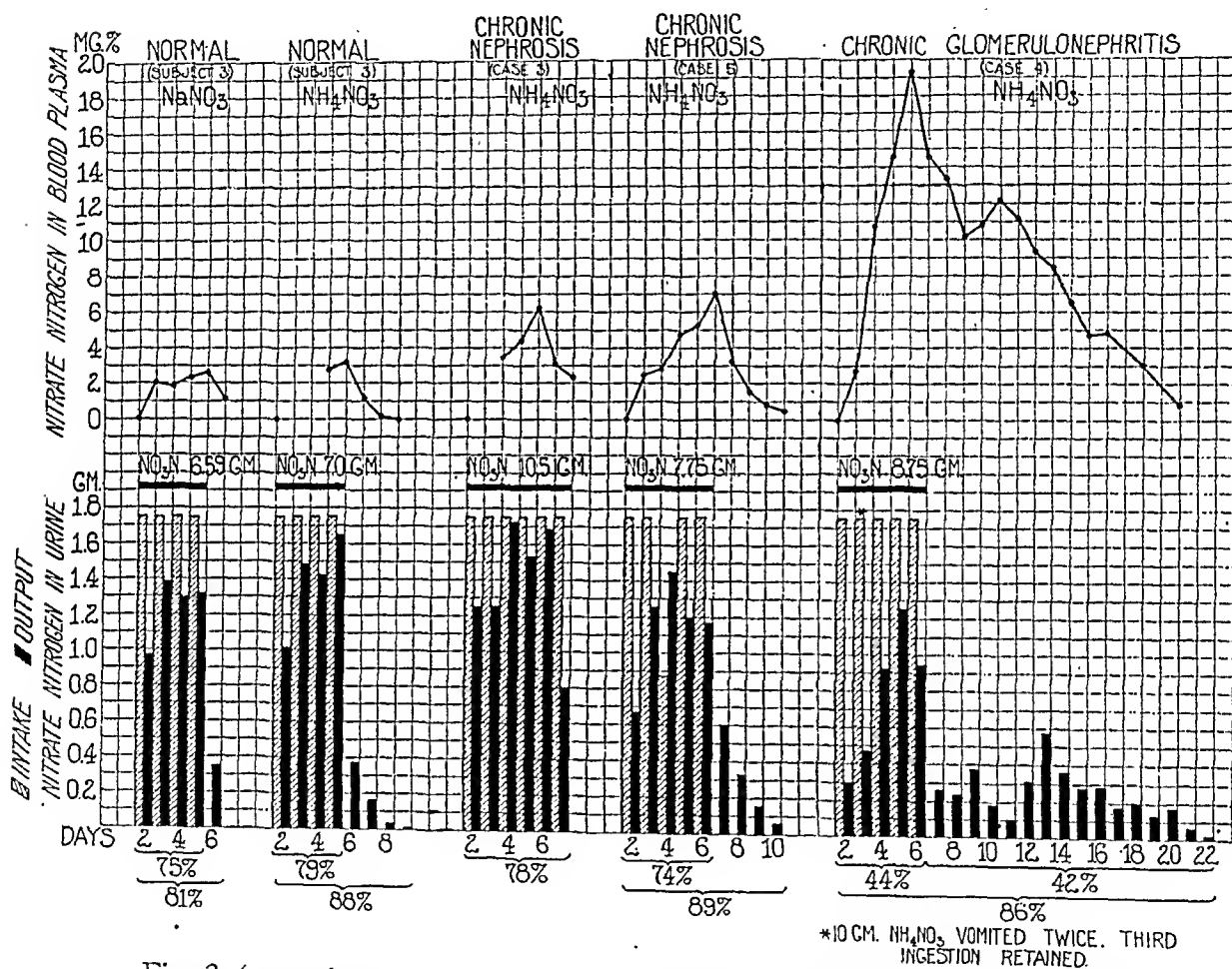


Fig. 2 (normal man 3, and cases 3, 4 and 5).—The effect of sodium nitrate and ammonium nitrate on the nitrate nitrogen of the blood plasma and the excretion of nitrate nitrogen in the urine is shown.

greater, so that a relative positive balance had occurred. In the experiments with sodium nitrate, a slightly negative balance ensued, whereas when ammonium acetate was employed, nitrogen equilibrium was maintained. Thus, in our study the nitrogen balance was variable, and only in a single experiment did retention of nitrogen occur.

The experiments on normal man 3, with sodium nitrate and ammonium acetate, were planned to determine the relative action of these salts in comparison with ammonium nitrate. The effect of sodium nitrate

TABLE 11.—*Mineral Metabolism (Normal Man 3)*

Blood*		Plasma		Urine										Comment		
Date, 1929	Hemo- globin, Gm. for Each 100 Cc.	Chloride Power, for Gm. for Each 100 Cc.	Carbon Dioxide Com- bining Power, for Gm. for Each 100 Cc.	Vol- ume, Cc.	pH	Chloride		Phosphorus		Sulphate as Sulphur Trioxide		Tetra- table Acidity, Cc. N/10	Total Fixed Base, Cc. N/10		Ammonia Nitrogen	
						Gm.	Cc. N/10	Gm.	Cc. N/10	Gm.	Cc. N/10				Gm.	Cc. N/10
5/20-21	1,000	6.6	3.2	900	0.74	238	1.48	390	152	1,610	0.42	300	9.62 Gm. ammonium acetate given†
5/21-22	725	6.6	1.38	388	0.60	194	1.18	295	116	1,135	0.25	179	
5/22-23	550	6.2	0.94	265	0.50	161	1.32	330	125	835	0.18	129	
5/23-24	17.1	376	60	450	5.8	0.59	166	0.59	191	1.46	365	194	770	0.21	150	
5/24-25	400	5.6	0.44	124	0.56	181	1.16	290	144	635	0.41	293	
5/25-26	475	5.6	0.33	93	0.80	258	1.53	382	247	730	0.49	350	9.62 Gm. ammonium acetate given
5/26-27	525	5.8	0.32	90	0.78	252	1.32	330	230	756	0.39	278	
5/27-28	17.1	...	61	500	5.6	0.25	71	0.77	248	1.67	417	240	720	0.35	250	9.62 Gm. ammonium acetate given, total 38.5 Gm.
5/28-29	475	5.6	0.33	93	0.72	232	1.53	382	227	640	0.42	300	

* Diet 4, additional water 800 cc.

† Given in 25 per cent solution.

TABLE 10.—Nitrogen Metabolism (Normal Man 3)

Date, 1923	Body Weight, Kg.	Nitrogen Intake			Blood*			Urine					Feces and Urine, Total Nitro- gen, Gm.	Comment
		Total, Gm.	Food, Gm.	Am- monia, Gm.	Non- protein Nitrogen, Mg. for Each 100 Gm.	Uren Nitro- gen, Mg. for Each 100 Gm.	Vol- ume, Cc.	Total Non- protein Nitro- gen, Gm.	Urea Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inine Nitro- gen, Gm.			
5/20	79.5	8.85	
5/20-21	78.7	9.6	1,000	8.85	6.4	0.42	0.75	9.60	
5/21-22	78.0	9.6	725	9.60	6.45	0.25	0.75	10.93	
5/22-23	77.3	9.6	550	8.15	5.90	0.18	0.72	8.40	Nitrogen balance (4 days), +0.6 Gm.
5/23-24	77.0	9.6	15	450	8.40	7.60	0.21	0.75	9.90	9.62 Gm. ammonium acetate given
5/24-25	76.8	11.35	9.6	1.75	400	9.90	6.80	0.41	0.76	12.05	9.62 Gm. ammonium acetate given
5/25-26	76.1	11.35	9.6	1.75	475	10.10	8.95	0.49	0.74	11.75	9.62 Gm. ammonium acetate given
5/26-27	76.4	11.35	9.6	1.75	525	11.75	10.25	0.39	0.73	12.64	9.62 Gm. ammonium acetate given; total 38.5 Gm.; nitrogen balance (4 days), -0.9 Gm.
5/27-28	76.1	11.35	9.6	1.75	33	22	500	10.90	9.85	0.35	0.75	1.74	10.50	
5/28-29	76.0	9.6	475	10.50	8.93	0.42	0.74		

... determined before breakfast at end of twenty-four hour period; diet 4, additional water 800 cc.

* Specimen of the blood taken
+ Given in 25 per cent solution.

taking it. Even after the ingestion of 10 Gm. of ammonium nitrate, a measurable amount could not be demonstrated in the feces; this indicates that absorption from the bowel was complete in this man.

CLINICAL USE IN CASES OF EDEMA

Method of Study.—In six cases of renal disease with edema, of which brief reports are appended, metabolic studies were done similar to those carried out on the four normal men. Some phase of metabolism of nitrates was studied, also, in twelve additional cases. The edema in these twelve patients was associated with renal or myocardial disease, cirrhosis of the liver, polyserositis or abdominal carcinomatosis. In the eighteen cases ammonium nitrate often was administered in enteric coated pills, each containing 0.5 Gm.⁴⁷ As the colorimetric method of Whelan for determining nitrates does not exclude the nitrites, care was taken that nitrites were not given for therapeutic purposes during these studies. An instance of a possible error of this sort was suggested in one case, for the patient had been given sodium nitrite for marked hypertension on the previous day. Estimations of certain constituents of the blood, urine and saliva were carried out as in the cases of the normal men. In a few cases, including case 5, the plasma chlorides were determined by the method of Wilson and Ball. This method, also, was applied to studies of the urine which contained protein. In addition, the concentration in the blood of creatinine nitrogen, protein, cholesterol and the content of water, as well as the concentration in the serum of total fixed base, sodium, potassium, calcium, magnesium, phosphorus and sulphate, were determined in some cases. The concentration of protein nitrogen in the urine was estimated. Simultaneous determinations were made of the concentration of nitrate nitrogen in the blood serum, edema fluid, fluid from the thoracic cavity and ascitic fluid both in cases of those patients who received and those who did not receive medication by nitrate.

In order to ascertain the actual amount of nitrate in the feces and to determine whether or not the presence of edema prevented digestion of the enteric coated pill or hindered absorption of ammonium nitrate from the bowel, estimations were made of nitrate in the feces, both before and after the ingestion of pills in four cases. In all, with the exception of one case, mere traces of nitrate were found. Possible failure to digest the coating of the pill or failure of absorption of nitrate in a single case would indicate that only rarely do untoward factors prevent ingested ammonium nitrate from entering the circulation. These results also show that excretion of nitrate by the bowel is minimal.

Action of Ammonium Nitrate.—The action of this substance on the blood was studied intensively in the six cases of renal disease with edema. In three instances the concentration of nitrate nitrogen in the plasma was determined. In two of the cases, of which reports are given at the end of this paper, (cases 3 and 5) and in which chronic nephrosis was present, the concentration of nitrate nitrogen in the plasma was as high as from 6 to 7 mg. in each 100 cc. This is distinctly higher than the concentration observed in the normal person, and yet urinary excre-

47. Enteric coated pills were used because nausea and vomiting less frequently follow their use. Ammonium nitrate in solution was troublesome in this respect.

been decidedly depleted so that in reality the diuretic effect of the ammonium nitrate and mersalyl was greater than the latter compound alone (fig. 3). This result is in accord with that obtained in the dog and also with that obtained in previous experiments with ammonium chloride and organic compounds of mercury.

Since inorganic nitrates are diffusible substances, it seemed important to determine their presence, and if they were found in a considerable

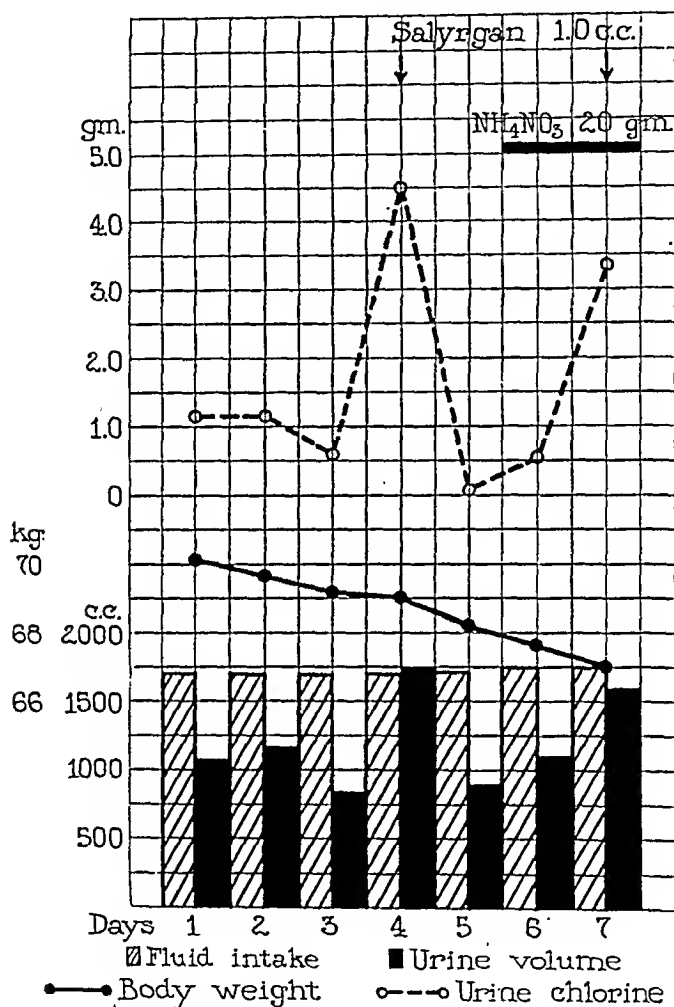


Fig. 3 (normal man 4).—The relatively greater effect of the combined action of mersalyl and ammonium nitrate than mersalyl (salyrgan) alone on the renal excretion of water and chloride is shown.

amount, it seemed advisable to determine their concentration in the saliva of normal persons. The concentration of nitrate nitrogen in the saliva was found to vary from 0.007 to 0.52 mg. in each 100 cc. This great variation in concentration possibly was due to differences in the diet and in the time of collection.

In normal man 2, the concentration of nitrate nitrogen in the feces was estimated both before he took ammonium nitrate and while he was

tion of a distinct increase in nitrate, a slight increase in protein, and a corresponding slight decrease in water content during the period of administration (table 12). In this case at least, with the increased nitrate content of the blood there was no change in many of the ions involved in the acid-base equilibrium. There was a slight reduction in water and an increase in protein that may have been due to a dehydrating effect of nitrate alone. Most of these patients with renal disease and edema retained nitrogen slightly during this period of ingestion of nitrate, and this may equally explain the increase in the concentration of serum protein. The effects on urinary excretion in these cases in which disease was present were similar to those seen in the normal men. There was a definite increase in volume and in the content of chlorides,

TABLE 12.—*Concentration of Serum Electrolytes Before and After the Administration of Ammonium Nitrate (Case 5) **

	Dec. 2, 1929		Dec. 7, 1929	
	Mg. for Each 100 Cc.	Millimols	Mg. for Each 100 Cc.	Millimols
Chloride.....	367	104	358	101
Phosphorus.....	4.2	4.1	3.9	3.9
Sodium.....	314	136	317	137.5
Potassium.....	†	20.3	6.6
Calcium.....	9.04	4.5	8.36	4.2
Magnesium.....	1.9	1.6	1.98	1.65
Sulphate.....	2.5
Carbon dioxide.....	64.7‡	30.5	64.2‡	28.9
Protein.....	4.3	4.8
Nitrate nitrogen.....	0.11	2.7	1.9
Water.....	94.6	93.2
Total fixed base (actual estimation).....	148

* 40 Gm. ammonium nitrate was given from Dec. 3, 1929, to Dec. 7, 1929.

† Determination not satisfactory.

‡ Per cent by volume.

nitrates and total fixed base. The increased hydrogen ion concentration and the increase in excretion of ammonia nitrogen were less evident. In a single case (case 3) the urinary sediment was examined daily and appreciable changes were not noted during the administration of ammonium nitrate. In case 2 the increased volume and the increased output of chloride continued for several days after the nitrate had been discontinued. On the other hand, in two cases during this second control period, there was a decrease in volume and concentration of chlorides comparable to that observed in the normal men. The slight increase in phosphate, sulphate and titratable acidity was even less than in the normal men.

The excretion of nitrate nitrogen in two cases of chronic lipid nephrosis (cases 3 and 5) was similar to that in normal persons, although there was a tendency for the excretion to lag during the second control period. In case 4, one of chronic glomerulonephritis, there was marked

tion was similar in both of these cases and in the normal person. The fall in the concentration of nitrate nitrogen was less rapid in case 5 than in the normal person. The observations in case 4, in which extensive edema was associated with chronic glomerulonephritis, are significant. There was obvious retention of nitrate, with a rapid rise of the concentration of nitrate in the plasma, to 19 mg. in each 100 cc. Instead of the usual rapid fall in the concentration of nitrate on discontinuing administration of ammonium nitrate, the decrease was slow and did not approach the normal value until the twentieth day. During this period, the concentration of nitrate in the edema fluid closely paralleled that of the plasma, and the daily urinary output was decreased and the total period of excretion of nitrate was prolonged. If we assume that only a very small amount of nitrate was absorbed before vomiting took place on the second day, approximately 86 per cent of the ingested salt was finally excreted during the period of twenty-two days.

The concentration of hemoglobin, as a rule, was little changed by administration of ammonium nitrate. In two experiments it was definitely increased. The concentration of urea nitrogen tended to remain stationary or fell. In case 4, there was a rise which undoubtedly was due to renal retention. The concentration of nonprotein nitrogen also tended to fall, except in two cases (cases 1 and 4). In case 1, the increase was not associated with a rise in urea, but with a diminished excretion of urinary protein, whereas in case 4 it was probably due to renal retention of urea. In two cases (cases 1 and 2), there was no significant change in the concentration of creatinine. The concentration of plasma chloride usually was increased, but varied little in the course of an experiment. In case 6, on one occasion, there was a distinct decrease. However, in this same case, the concentration of chloride in the edema fluid was very constant. As in the normal man, there was no significant change in the carbon dioxide combining power of the plasma. The amount of the total fixed base was determined on several occasions in case 5. There was a decrease from a high concentration in the control period in one experiment, and practically no change in another.

In order to test further the possible acid-base changes in blood serum or plasma, detailed quantitative analysis of certain constituents was made before and during the administration of nitrate. The patient (case 5) was selected for this study on his second admission, because of his previous good response to ammonium nitrate. The amounts of nitrate ingested and excreted in the urine were comparable to those ingested and excreted on the previous admission. The results of analysis of serum on both occasions were approximately identical, with the excep-

TABLE 13.—*Nitrogen Metabolism (Case 5)*

Date, 1929	Body Weight, Kg.	Nitrogen Intake			Blood*				Urine					Urine and Feces, Total Nitro- gen, Gm.	
		Total, Gm.	Food, Gm.	Am- monia, Gm.	Non- protein Nitro- gen, Mg. for Each 100 Gm.	Urea Nitro- gen, Mg. for Each 100 Gm.	Total Nitro- gen, Fixed gen, Mg. for Each 100 Gm.	Total Nitro- gen, (Kjel- dahl)	Pro- tein Nitro- gen, Gm.	Total Non- protein Nitro- gen, Gm.	Am- monia Nitro- gen, Gm.	Creat- inine Nitro- gen, Gm.			
7/22	18	...	0.04	
7/23-24	72.7	9.6	750	1.85	10.95	0.65	0.49	0.75	1.73	14.53
7/24-25	72.7	9.6	500	9.1	7.35	6.85	0.24	0.53	1.21	10.31
7/25-26	72.7	9.5	175	580	11.95	10.05	7.90	0.34	0.56	1.27	13.22
7/26-27	72.3	9.5	50	20	...	550	11.0	2.15	7.70	0.37	0.53	0.67	11.67
Nitrogen balance (4 days), daily average, -2.9 Gm.															
7/27-28	71.4	13.1	9.6	1.75	900	1.50	10.80	9.00	0.42	0.58	1.06	13.36
7/28-29	71.1	13.1	9.6	1.75	1,025	1.12	11.68	9.65	0.25	0.56	0.89	13.69
7/29-30	70.0	11.3	9.6	0.875	950	0.85	10.45	8.45	0.98	0.49	1.72	13.02
5 Gm. ammonium nitrate, vomited															
7/30-31	70.0	13.0	9.5	1.75	875	0.90	10.30	8.92	0.78	0.46	1.30	12.50
7/31-8/1	69.1	13.0	9.5	1.75	47	18	160	925	1.10	11.30	9.35	0.83	0.52	0.92	13.32
10 Gm. ammonium nitrate															
10 Gm. ammonium nitrate, total 45 Gm., 74 per cent nitrate ingested excreted in urine, nitrogen balance (5 days) daily average, -2.0 Gm.															
8/1-2	69.5	9.5	675	0.75	8.90	6.65	0.88	0.50	2.48	12.13
8/2-3	70.4	..	9.6	600	0.60	8.60	6.75	0.90	0.54	1.19	10.39
8/3-4	70.5	9.6	450	1.20	7.15	5.23	0.86	0.43	1.68	10.03
8/4-5	70.0	9.6	0.5	650	1.10	9.90	8.45	1.15	0.53	1.06	12.06
Nitrogen balance (4 days) daily average, -1.6 Gm., 89 per cent nitrate ingested excreted in urine															

Nitrogen balance (4 days), daily average, -2.9 Gm.
 10 Gm. ammonium nitrate†
 10 Gm. ammonium nitrate
 5 Gm. ammonium nitrate, 5 Gm. vomited‡
 10 Gm. ammonium nitrate
 10 Gm. ammonium nitrate, total 45 Gm., 74 per cent nitrate ingested excreted in urine, nitrogen balance (5 days) daily average, -2.0 Gm.

Nitrogen balance (4 days) daily average, -1.6 Gm., 80 per cent nitrate ingested excreted in urine

* Specimen of the blood taken and body weight determined before breakfast at end of twenty-four hour period.

† Given in 25 per cent solution.

‡ Patient vomited 20 cc. of 25 per cent solution (5 Gm.) immediately after ingested, diet 2, additional daily water 600 cc.

delay, with a resulting prolonged diminished daily output. In spite of this retention of nitrate, there was an initial increase in volume of urine, and in output of chlorides and of total fixed base. It was anticipated that retention of nitrate might occur in this case because there were other evidences of diffuse renal injury, for example, excretion of phenolsulphonphthalein of only 10 to 15 per cent in two hours and a somewhat fixed excretion of several urinary constituents. However, retention of nitrate to such a degree naturally was not expected.

One of the most specific effects of nitrates has been the excretion of chloride, fixed base and ammonia, when ammonium nitrate is administered. The increased excretion of both nitrate and chloride indicates that the tissues must neutralize two strong acids. Hence, with the administration of sodium nitrate there is a definite increase in fixed base, but the excretion of ammonia is not increased (normal man 3, tables 8 and 9). With ammonium nitrate, however, there is always a marked increase in both the excretion of fixed base and ammonia (normal man 3, tables 6 and 7, and case 5, tables 13 and 14). Averaging results over the entire period of ingestion of ammonium nitrate, the greater part of the acid is neutralized by ammonia. However, the available fixed base somewhat determines the degree to which the excess acid is neutralized by ammonia, as the figures for neutralization for each day will show. Calculations according to Fiske's⁴⁸ plan and figures, obtained from the three experiments, two of which were on subject 3, one on case 5 (tables 6, 7, 8, 9, 13 and 14), show that with the use of ammonium nitrate, from none to 60 per cent of the nitrate is bound by base and from 30 to 80 per cent by ammonia, whereas, with the use of sodium nitrate, practically all the nitrate is bound by fixed base, presumably from the sodium of the administered salt. Folling has shown that after the ingestion of ammonium chloride, a high percentage of the ingested chlorine is neutralized by ammonia.

The total nonprotein nitrogen, and the urea and ammonia fractions, were not uniformly increased by ingestion of ammonium nitrate. The excretion of ammonia nitrogen was prolonged in cases 1, 2 and 5, as in the normal men, but in case 4 it was scarcely altered from that of the control period in the same case. The concentration of creatinine nitrogen as a rule was constant, but in some cases the daily variation was greater than that found in normal persons. The excretion of protein nitrogen was variable; in some cases it increased; in others, it diminished. In two cases in which the concentration of urinary protein was diminished,

48. Fiske, C. H., and Sokhey, S. S.: Ammonia and Fixed Base Excretion After Administration of Acid by Various Paths, *J. Biol. Chem.* **63**:309 (March) 1925.

the concentration of nonprotein nitrogen of the blood was increased or remained elevated. The ratio of inorganic sulphate to total nitrogen was approximately constant.

Studies of nitrogen balance were carried out in five cases during an initial control period. In case 1 the condition was one of nitrogen equilibrium; in cases 3 and 4 the condition was one of positive balance, whereas in cases 2 and 5 (table 5) it was one of negative balance. These variable phenomena, in cases of edema, are comparable with those observed in the normal subjects and emphasize the importance of an initial control period before the attempt is made to determine the effect of the test substance. During the ingestion of ammonium nitrate in cases 2 and 5, the negative balance decreased, or, in other words, a relative positive balance had developed; in case 1 there was an actual positive balance, and in case 4 the previous positive balance continued to be present. These results in cases of edema indicate that during the ingestion of ammonium nitrate there is usually absolute or relative retention of nitrogen. In case 4 this probably was due to continued retention of urea; in case 1, to retention of both urea and urinary protein, and in cases 2 and 5 to storage of nitrogen in the extrarenal tissues. There is now good evidence that extrarenal storage of nitrogen occurs in many cases of renal edema. This is particularly true after diuresis has occurred and convalescence is established.

After ingestion of ammonium nitrate, the concentration of nitrate in the saliva was definitely increased above the normal, as was noted by Ville and Mestrezat⁴⁹ after administration of sodium nitrate, but the concentration was much less in degree in the saliva than in the urine.

The comparative concentrations of nitrate nitrogen in the blood plasma or serum and in edema fluid, fluid from the thoracic cavity and ascitic fluid were determined in several cases of edema, both before and during the administration of ammonium nitrate. Similar concentrations were the rule, but occasionally there were measurable differences. These observations emphasize that nitrates penetrate readily into the tissues of the whole body, a property that might be expected of such readily soluble and diffusible salts.

Toxic Effects.—Toxic symptoms due to abnormally large doses of nitrates, particularly potassium nitrate, have been reported repeatedly since Alexander's description⁵⁰ in 1773. The use, twenty years ago, of bismuth subnitrate in large amounts, for diagnostic purposes, led to

49. Ville, J., and Mestrezat, W.: Origine des nitrites contenus dans la salive; leur formation par réduction microbienne des nitrates éliminés par ce liquide, *Compt. rend. Soc. de biol.* **63**:231 (July) 1907.

50. Alexander, William, quoted by Jörg (footnote 2).

tioned by subjects used as normal controls or by patients. Caution must be used in giving any ammonium salt to a patient with an abnormally high concentration of blood urea. This danger signal we previously emphasized when advocating the use of ammonium chloride.⁵⁵ With the usual rapid excretion of nitrate in the urine, toxic symptoms rarely occur.

The toxic features that developed in case 4, during marked retention of nitrate, are of great interest. The patient's symptoms were headache, asthenia, nausea, vomiting and drowsiness, and at times mild delirium was present. Similar toxic gastro-intestinal symptoms were graphically described by Alexander, in 1773, in the case of a woman who had taken a massive dose of potassium nitrate. The blood pressure, which previously had averaged 155 systolic, and 100 diastolic, was increased to 200 systolic and 125 diastolic, and remained thus elevated for ten days during the period of retention of nitrate. Cyanosis, such as one observes in methemoglobinemia, was not present, nor were severe retention of urea and acidosis present. The possibility of increased concentration of ammonia in the blood and tissues could not be excluded, although a concentration high enough to produce toxic symptoms seems unlikely. These observations support the view that the toxemia was caused by the nitrate ion. Prompt estimation of nitrate in the blood should give early warning and should prevent marked retention of nitrate such as that which occurred in a single case of this series.

Long-continued daily ingestion of doses of from 8 to 10 Gm. was carried out in three cases without any toxic manifestations. The total amount ingested in these three cases was 250 Gm. in twenty-five days, 478 Gm. in fifty-six days, and 295 Gm. in thirty days. As much as 560 Gm. was administered to the latter patient during the entire period of hospital treatment, without toxic symptoms.

COMMENT

These studies show that nitrates are efficient diuretics. The diuretic response is accompanied by certain specific metabolic changes which involve the inorganic salts, the acid-base equilibrium, water balance and the nitrogen balance. The best results were obtained by the use of ammonium nitrate, apparently because, on absorption, the ammonium radical is readily converted into urea, leaving the nitrate portion of the

55. Keith, N. M.; Barrier, C. W., and Whelan, Mary: The Diuretic Action of Ammonium Chlorid and Novasurol in Cases of Nephritis with Edema, *J. A. M. A.* **85**:799 (Sept. 12) 1925.

several cases of nitrate poisoning accompanied by methemoglobinemia.⁵¹ Since the introduction of ammonium nitrate as an effective diuretic four years ago, the drug has been taken by several normal persons and by a large number of patients in doses of 6 to 10 Gm. daily, with remarkably few toxic manifestations. Christian,⁵¹ and Barker and O'Hare,⁵² in 1928, reported cyanosis and methemoglobinemia without other toxic symptoms, in a patient with nephritis and edema who was receiving 15 Gm. of ammonium nitrate daily. Since May, 1928, we have observed the occurrence of cyanosis and methemoglobinemia in three patients who were receiving diuretic treatment including ammonium nitrate. The results in two cases were reported by Eusterman and Keith⁵³ in 1929. One of these patients received, at another time, 24 Gm. of ammonium nitrate over a period of three days, and again methemoglobinemia was produced. Striking untoward symptoms did not develop, and cessation of administration of the drug led to rapid disappearance of the cyanosis and methemoglobinemia. The third patient, one with chronic nephrosis, received 10 Gm. daily and the same untoward conditions developed after ingestion of approximately 122 Gm. In all three cases definite dysfunction of the intestine was present in the form of chronic obstruction or marked constipation. This fact leads one to consider the possibility of some abnormal function, such as bacterial action in the intestine, which could cause reduction of the nitrate to nitrite, and the formation of methemoglobin. On the other hand, the lack of cyanosis in case 4, in which there was marked retention of nitrate for several days, indicates that nitrates in considerable amounts may be widely distributed throughout the body without giving rise to gross methemoglobinemia. Similarly, nitrites may be present without methemoglobinemia developing, for Binz⁵⁴ showed that sodium nitrite could be given experimentally in doses large enough to produce a narcotic-like action, without change in the color of the blood.

Minor toxic symptoms, such as nausea and vomiting, occasionally appeared shortly after small amounts of the drug had been given in solution. This observation led to the use of enteric coated pills, which have proved to be more satisfactory. Diarrhea has scarcely been men-

51. Christian, H. A.: Discussion, *Tr. A. Am. Phys.* **43**:290, 1928.

52. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, *J. A. M. A.* **91**:2060 (Dec.) 1928.

53. Eusterman, G. B., and Keith, N. M.: Transient Methemoglobinemia Following Administration of Ammonium Nitrate, *M. Clin. North America* **12**:1489 (May) 1929.

54. Binz, C.: Ueber einige neue Wirkungen des Natriumnitrits, *Arch. f. exper. Path. u. Pharmacol.* **13**:133 (Oct.) 1881.

effects often were slower in beginning, but once started were, as a rule, more prolonged. In some instances, active diuresis persisted for several days after ingestion of ammonium nitrate was discontinued. These results indicate that the rapidity and extent of the action of nitrate depend in part on the amount and composition of the edema fluid, and also on the degree of restoration of the normal current of fluid from tissues to blood and from blood to urine. When severe renal injury is present, marked retention of nitrate may occur and may cause specific toxic symptoms.

The disturbance of the acid-base equilibrium is of interest. The bicarbonate of the blood plasma is not reduced. The initially increased urinary excretion of acid radicals is accompanied by a relatively larger amount of fixed base than of ammonia, but with continued action, the amount of fixed base diminishes as that of ammonia proportionately increases.

Keith and Whelan,⁶ and Folling, after ingestion of ammonium chloride, and Gamble and his co-workers, after ingestion of calcium chloride, have demonstrated urinary data similar to those observed after ingestion of ammonium nitrate. However, Folling concluded that the diuresis occurred only when the increased acid was neutralized by a relatively large proportion of fixed base. Both with ammonium chloride and ammonium nitrate, we are unable to find such an exact relationship. The different specific biochemical effects of two inorganic anions, such as chloride and nitrate, are of significance. Both produce changes in the acid-base equilibrium. The nitrate causes much less change in the bicarbonate of the blood than the chloride, and yet the diuresis produced is greater.

Both relative and actual retention of nitrogen may occur. Two causative factors at least must be considered: (1) diminished ability of the kidney to excrete urea or protein, and (2) actual retention of nitrogen in the tissues due to extrarenal factors.

The actual site of the diuretic action of nitrates is not definitely known. If their action is entirely renal, the loss of water and salts eventually affects the general tissue metabolism. The present studies indicate that their action is a combined one and that they affect both the kidneys and the tissues generally. Primarily, the nitrate ion would appear to have a specific action on the tissues, which causes liberation of water and chlorides. This effect, in our opinion, is not entirely due to increase in hydrogen ion concentration, as has been suggested for ammonium chloride, nor does it seem to be a simple substitution of nitrate for chloride, similar to that of iodide or bromide for chloride.

molecule free to act. The concentration of nitrate in the blood rises considerably, and nitrate is readily excreted by the kidney. In man, as much as 90 per cent of the nitrate ingested has been recovered in the urine, indicating that only small amounts are excreted through other channels or are taken care of by the organism in other ways. The smaller amount excreted by the dog in our experiments may be due to the fact that administration was by the intravenous route or because sufficient time was not allowed for excretion. These results suggest that nitrate might be usefully employed as a test of renal function. In contrast to the results obtained by Mitchell, Shonle and Grindley,⁵⁶ there is little evidence in our experiments that considerable amounts of nitrate are destroyed in the human body. In our work, as in that previously done by others, systemic nitrite-like actions did not occur, with the exception of the rare development of methemoglobinemia. Thus, the reduction of nitrates to nitrites rarely occurs in animals, although Kastle and Elvove⁵⁷ have shown that certain extracts of plants in vitro have reducing action. The increased concentration of nitrate in the saliva is evidence of its diffusibility and possible wide distribution throughout the body. Nitrates cause disturbance of the metabolism of inorganic salts, especially of the chlorides. It is of interest that an increased concentration of one anion (nitrate) should cause increased excretion of another anion (chloride). The retention of salts is similar to that following the diuresis produced by many other substances.⁵⁸ The disturbance in the acid-base equilibrium toward the acid side is not sufficiently great in man to produce significant reduction in the carbon dioxide combining power of the plasma, but it does cause an increase in the hydrogen ion concentration of the urine, and a markedly increased excretion of fixed base and ammonia. In a single experiment retention of nitrogen occurred.

The action of ammonium nitrate in cases of edema was similar to but not as uniform as its action in the normal subject. The concentration of nitrate in the blood rose to a higher level, and the excretion in the urine was not so rapid. The content of nitrate in edema fluid usually closely paralleled that of the blood plasma. The diuretic and metabolic

56. Mitchell, H. H.; Shonle, H. A., and Grindley, H. S.: The Origin of the Nitrates in the Urine, *J. Biol. Chem.* **24**:461 (April) 1916.

57. Kastle, J. H., and Elvove, Elias: On the Reduction of Nitrates by Certain Plant Extracts and Metals, and the Accelerating Effect of Certain Substances on the Progress of Reduction, *Am. Chem. J.* **31**:606, 1904.

58. Keith, N. M., and Whelan, Mary: Changes in Body Temperature and Metabolism Accompanying Experimental Marked Diuresis, *Am. J. Physiol.* **77**: 688 (Aug.) 1926.

CASE 1.—A woman, aged 40, came to the clinic on Oct. 16, 1927, with the complaint of dropsy. In 1919, she had had edema of the lower part of the legs for three months. The present illness had begun two months previously, with dependent edema, which gradually spread over the whole body. General examination showed moderate general edema, most marked in the dependent parts. Definite objective abnormalities in the cardiovascular system were not observed. The blood pressure was 140 systolic and 90 diastolic. The ocular fundi were normal. Urine showed marked albuminuria with a few erythrocytes, leukocytes and double refractive lipid substances. The blood urea nitrogen was 10 mg., the blood creatinine 1.2 mg., serum proteins 3.6 Gm., with 50 per cent albumin, and blood cholesterol 500 mg. in each 100 cc. The hemoglobin (Dare) was 70 per cent; erythrocytes numbered 4,130,000. The excretion of phenolsulphonphthalein was 45 per cent in two hours. During the period of treatment in the hospital, the edema disappeared, with a loss of 9 Kg. in body weight.

The patient returned for examination in June, 1928. The blood pressure was 150 systolic and 105 diastolic; erythrocytes numbered 3,670,000. The ocular fundi showed changes of hypertension in the retinal arteries and one resolving exudate. The subsequent course was that of slowly progressive failure, and the patient died on April 6, 1929. The diagnosis was chronic glomerulonephritis.

CASE 2.—A colored man, aged 30, registered at the clinic on Dec. 30, 1927. Two and a half years previously, edema of the face and legs, hematuria, albuminuria and oliguria had developed; the illness lasted for three weeks, and he thought that he had recovered from it. Two and a half months before admission, edema had begun, and in a short time general anasarca developed. Dyspnea, oliguria and hematuria were also present. On general examination there was orthopnea and marked general anasarca, left hydrothorax and ascites. The blood pressure was 170 systolic and 120 diastolic. The ocular fundi were essentially normal. The urine contained large amounts of albumin, a few casts, leukocytes and double refractile bodies, but no erythrocytes. The hemoglobin (Dare) was 73 per cent; erythrocytes numbered 3,850,000. The Wassermann reaction of the blood was strongly positive. The blood urea nitrogen was 15 mg., creatinine 2 mg., serum proteins 3.3 Gm., of which 38 per cent was albumin, and the blood cholesterol, 338 mg. The excretion of phenolsulphonphthalein was 40 per cent in two hours. During treatment in the hospital with ammonium nitrate and mersalyl, striking and lasting diuresis occurred, with the disappearance of the edema and a loss of 37.6 Kg. in body weight. The diagnosis was chronic glomerulonephritis with anasarca.

CASE 3.—A girl, aged 15, was admitted to the clinic on April 11, 1929. Two and a half months before admission, the patient had had an acute sore throat for five days. Two weeks later she noticed the gradual onset of generalized edema which became marked and resistant to treatment. She had gained 16 Kg. since the onset of the illness. General examination showed general anasarca. The tonsils were enlarged and infected. The ocular fundi were normal. The blood pressure was 120 systolic and 80 diastolic. Urinalysis showed marked albuminuria and some casts, but no blood cells. Hemoglobin (Dare) was 70 per cent; erythrocytes numbered 4,400,000. The blood urea nitrogen was 6 mg., creatinine 1 mg., serum proteins 3.3 Gm., of which 46 per cent was albumin, and blood cholesterol 501 mg. Following treatment in the hospital for one month, the edema disappeared and loss in weight amounted to 11.8 Kg. Two days after tonsillectomy, fever developed and later there was evidence of general peritonitis and septicemia. The patient died on the fifth day after tonsillectomy. At necropsy,

Loewi⁵⁹ suggested that such a substitution takes place, but Sollman⁶⁰ and Cushny,⁶¹ with both of whom we agree, do not believe the experimental data can be fully explained on this basis. If a specific effect on the cells and tissues does occur, conceivably metabolism of protein could be affected, and thus the altered excretion of nitrogen, sulphate and phosphate sometimes observed in our experiments could be explained. It might also explain the initiation of the accelerated current of fluid from tissue to blood and from blood to urine. Such a possible process is in harmony with the demonstration by Curtis⁶² that intraperitoneal injections of certain solutions may profoundly alter the diuretic response to administration of caffeine to rabbits.

Schlosser,⁶³ in 1913, showed experimentally that the combined use of caffeine and sodium sulphate produced greater diuresis than either of these substances alone. Similar results were obtained by us with ammonium chloride and with an organic compound of mercury, and in this study, also, by ammonium nitrate and organic compounds of mercury. Both of these ammonium salts, organic compounds of mercury, and caffeine cause a saline type of diuresis. Further combinations of diuretics should prove to be of theoretic interest, and possibly should lead to greater beneficial results in the treatment of dropsy.

Toxic phenomena rarely have occurred. The use of enteric coated pills containing ammonium nitrate has lessened the occurrence of nausea and vomiting. When the rare instances of methemoglobinemia do occur, there are no annoying subjective or toxic symptoms, and simple withdrawal of the drug results in rapid disappearance of the cyanosis. The occurrence of actual toxic effects from too high a concentration of nitrate in the body fluids can be avoided. Effective measures against toxic effects are preliminary tests of renal function and, on the first suspicion of toxemia, estimation of the nitrate content of the blood.

REPORT OF CASES

Following are brief reports of the six cases in which complete metabolic studies were made.

59. Loewi, Otto: Untersuchungen zur Physiologie und Pharmakologie der Nierenfunction, Arch. f. exper. Path. u. Pharmacol. **48**:410 (Dec.) 1902.

60. Sollman, Torald: The Effect of Diuretics, Nephritic Poisons and Other Agencies on the Chlorides of the Urine, Am. J. Physiol. **9**:425 (Aug.) 1903.

61. Cushny, Arthur R.: The Secretion of the Urine, ed. 2, New York, Longmans, Green & Company, 1926, pp. 189-190.

62. Curtis, G. M.: Die Wirkungsweise der spezifischen Diuretica nebst Beiträgen zur Lehre von der Harnabsonderung, Biochem. Ztschr. **163**:109, 1925; Die Wirkungsweise der spezifischen Diuretica, Klin. Wchnschr. **4**:824 (April) 1925; The Action of the Specific Diuretics, J. A. M. A. **93**:2016 (Dec. 28) 1929.

63. Schlosser, K.: Ueber die Wirkung kombinierter Diuretica, Ztschr. f. d. ges. exper. Med. **1**:559, 1913.

SUMMARY

The diuretic action of nitrates has been confirmed by the extensive use of ammonium nitrate. The action involves certain specific metabolic changes which result from the liberation of salts and water from the tissues. Nitrate reaches a considerable concentration in the blood and edema fluid, and is readily excreted by normal kidneys and by those which have undergone certain pathologic changes. Rare toxic conditions can be prevented or effectively treated. Further diuretic action can be obtained by combining the administration of nitrate with that of other diuretics.

general peritonitis was found; the kidneys together weighed 423 Gm. and resembled the large pale kidneys of chronic nephrosis. Microscopic study showed the characteristic changes of chronic nephrosis without definite glomerulonephritis.

CASE 4.—An unmarried woman, aged 24, registered at the clinic on May 21, 1929. Eight months previously she had first noticed edema of the feet, and general anasarca subsequently developed rapidly. On general examination, the mucous membranes were pale, and extreme general anasarca was present. The ocular fundi showed some neuroretinal edema. The blood pressure was 170 systolic and 120 diastolic. Urinalysis showed a high content of albumin and many casts, but no erythrocytes. The hemoglobin (Dare) was 50 per cent; erythrocytes numbered 2,800,000. The blood urea nitrogen was 11 mg., serum proteins 3.2 Gm., of which 30 per cent was albumin, and blood cholesterol 398 mg. The excretion of phenolsulphonphthalein was 15 per cent in two hours. Following the use of ammonium nitrate, diuresis resulted, but within a few days toxic manifestations developed and the drug was discontinued. At the time of dismissal, eighty-five days after admission, the patient was almost free from edema, having lost 37 Kg. in weight. The diagnosis was chronic glomerulonephritis with anasarca. The prognosis was guarded.

A second examination was made on Nov. 4, 1929. There had been definite improvement. The blood pressure was 130 systolic and 90 diastolic. The blood urea nitrogen was 16 mg. The excretion of phenolsulphonphthalein was 25 per cent in two hours. A letter in March, 1930, stated that the patient is still improving.

CASE 5.—A man, aged 24, registered at the clinic on July 16, 1929. He had first noticed edema in March, 1929, which gradually became generalized, and which persisted until admission. General examination showed marked general anasarca. The ocular fundi were normal. The blood pressure was 130 systolic and 90 diastolic. Urinalysis showed a high content of albumin, some casts and a few leukocytes, but no erythrocytes. The hemoglobin (Dare) was 75 per cent; erythrocytes numbered 4,430,000. The blood urea nitrogen was 22 mg., the creatinine 1.5 mg., the serum proteins 3.6 Gm., of which 39 per cent was albumin, and the blood cholesterol 337 mg. The excretion of phenolsulphonphthalein was 65 per cent in two hours. Following treatment, the edema disappeared, with a loss of 18 Kg. in weight. The diagnosis was chronic lipid nephrosis.

A second examination was made on Dec. 2, 1929. There was slight recurrence of edema and a recent infection of the upper respiratory tract. The data were essentially the same as before. A third examination was made on Feb. 5, 1930. Edema or anemia was not present. The other data were the same as on the former visits.

CASE 6.—A man, aged 47, was admitted to the clinic on Jan. 23, 1928. There had been gradual development of edema which had begun four months previously. On general examination there was moderate general anasarca and some ascites. The blood pressure was 120 systolic and 90 diastolic. The ocular fundi appeared normal. The urine contained a large amount of albumin, numerous casts, a few leukocytes and double refractive bodies, but no erythrocytes. The hemoglobin (Dare) was 70 to 75 per cent; erythrocytes numbered 4,000,000. The blood urea nitrogen was 12 mg., blood creatinine 1.8 mg., serum proteins 3.5 Gm., of which 44 per cent was albumin, and blood cholesterol 309 mg. The excretion of phenolsulphonphthalein was 65 per cent in two hours. During treatment, the edema disappeared and the patient lost 13.6 Kg. in weight. The diagnosis was chronic lipid nephrosis.

His father and mother were living and in good health. There was no history of tuberculosis, diabetes, nervous diseases, mental disorders, cancer, hemophilia or goiter in the family.

Physical Examination.—The patient was moderately undernourished; he was not acutely ill nor in evident distress. The weight could not be secured on account of the paralysis of the legs. The temperature was 98.6 F.; the pulse rate 90, and respirations 16 to the minute.

The hair was sparse and dark and was of the average quality and texture. The skin was smooth, warm and rather moist. It was unusually shiny over the lower half of the arms and legs.

The pupils reacted well to light and in accommodation. The extra-ocular movements were normal. Ophthalmoscopic examination showed the media to be clear, the outlines of the disks sharp, normal cupping and the usual retinal observations.

There was bilateral, partial deafness. A slight amount of mucopurulent discharge came from the left ear. The Weber test was lateralized to the left. Bone conduction was better than air conduction on the two sides.

The sense of smell was unimpaired. Nothing unusual was observed in the nasal cavities.

The gums showed a rather widespread active pyorrhea. Several teeth appeared to be devitalized. The tonsils were small, scarred and embedded and showed moderate retention. Pus was easily expressed from the left side. The pharynx was moderately congested, and some mucopurulent material adhered to the posterior pharyngeal wall.

There was no general glandular enlargement. The anterior cervical glands draining the tonsils were enlarged. The axillary, inguinal and epitrochlear glands were not palpable.

The thyroid gland was small and deeply set. No nodules were felt.

The chest was narrow and of the asthenic type. Expansion was good. The bases of the lungs descended equally on the two sides. Litten's sign was positive bilaterally. There was some impairment of the percussion note over the left upper part of the chest posteriorly. Tactile and vocal fremitus were considered normal. The breath sounds were unimpaired, except for questionable muffling over the left upper posterior portion of the chest. No posttussic râles were elicited in the upper half of either lung.

The apex impulse of the heart was not visible but was palpable in the fifth intercostal space, 8 cm. from the left of the midsternal line. Dulness extended 9 cm. to the left and 2 cm. to the right. The heart tones were of good quality, and the rhythm was regular. No murmurs or accentuations were heard. The pulse rate was 80 to the minute and was of good volume and tension. The arterial walls were not thickened. The blood pressure was 158 systolic and 100 diastolic.

The abdomen was ovoid, soft and relaxed. The liver and spleen were not felt. There was slight tenderness over the transverse colon. No herniations or ascites were present. Posteriorly, there was deep tenderness to massive percussion over the right kidney.

The right testicle was retracted, and there was a small hard nodule in the region of the globus major. The left testicle was considered normal. The prostate was of normal size, shape and consistency.

There was a flaccid motor paralysis of the lower extremities. The arms could be moved but very weakly, especially at the wrist. Movement was slightly stronger at the elbows and the shoulders. There was a peculiar gloss to the skin of the

PERIPHERAL NEURITIS COMPLICATED BY MASSIVE COLLAPSE OF THE LUNG FOLLOWING TONSILLECTOMY*

HAROLD V. DWYER, M.D.

DETROIT

The following case is submitted because of a threefold point of interest, i. e.: (1) the development of a multiple peripheral nerve paralysis in the presence of an existing renal tuberculosis; (2) the occurrence of massive collapse of the lung following tonsillectomy, and (3) the clearing up of the paralyses following removal of the foci of infection.

REPORT OF CASE

History.—A white man, aged 39, an ironworker, entered the hospital on Aug. 31, 1928, complaining of weakness of the arms and paralysis of the legs of a gradually progressive nature. He dated the onset of his symptoms about two and a half months prior to his admission, and stated that it followed his recovery from an attack of left lobar pneumonia. The early symptoms consisted of a tingling sensation in the fingers and toes followed in three weeks by weakness, which first appeared in the knees. A gradually increasing loss of strength developed in the legs and started in the arms. Ten days prior to admission, he lost the use of his legs entirely. Meanwhile the loss of power in the arms continued, and at the time of admission he could move the fingers and arms, but had very little strength in them.

Two years previously a diagnosis of renal tuberculosis on the right side had been made, and at that time tubercle bacilli had been demonstrated in the urine. Operation for the removal of this kidney was advised but was refused, and no other treatment had been instituted in the interval. The only symptom he complained of relative to the kidneys at this time was a frequency of urination.

He had had measles in childhood, influenza in youth and lobar pneumonia in May, 1928, prior to the present illness. There was no history of injuries or operations.

The patient said that he was an ironworker and had been for six years. This work required fairly heavy physical exertion. He secured an abundance of outdoor exercise and fresh air. He was accustomed to eight or nine hours of sleep at night and usually rested well. Coffee and tobacco were used in moderation and alcohol rarely. His average weight was given as 135 pounds (61.2 Kg.); he had lost approximately 15 pounds (6.8 Kg.) during his recent illness.

There were no symptoms referable to the cardiovascular or gastro-intestinal system. Frequency of urination, urgency, nocturia and cloudy urine were present at irregular intervals for two years.

* Submitted for publication, April 7, 1930.

* Read before the Henry Ford Hospital Medical Society, Detroit.

* From the Department of General Medicine, Henry Ford Hospital.

Progress.—The temperature remained normal or below for thirty days. The pulse rate ranged between 80 and 100. The respirations ranged from 16 to 20.

The patient was given general upbuilding therapy, i. e., rest in bed, high caloric diet, treatments with the ultraviolet light and physical therapy. The weakness of the arms progressed for the first two weeks. This continued until the hands could just be moved, then the condition became stationary. At this time all the devitalized and suspicious teeth were extracted. The patient was transferred to the nose and throat division one week later, where a tonsillectomy was performed under local anesthesia.

On the morning of the first day following the operation, he experienced an acute attack of dyspnea accompanied by palpitation and cyanosis. The pulse rate rose to 130 and a few hours later to 160. The temperature rose to 100 F. The dyspnea and cyanosis increased until the condition became alarming. The patient was in acute distress, panting for breath and very cyanotic. There was infrequent coughing, with expectoration of small mounts of tenacious mucoid sputum. No pain was experienced. The chest showed limitation of motion on the left side. There was hyperresonance to percussion over the right side, and many coarse moist râles were heard anteriorly below the level of the third rib. The lower left side of the chest exhibited distant breath sounds and impaired resonance. The apex impulse of the heart was forceful and heaving and was visible and palpable in the left anterior axillary line in the fourth interspace. The cardiac dullness extended 14 cm. to the left of the midsternal line and merged with the impaired resonance already noted in the lower left side of the chest. The right border of the heart was not percussable due to the hyperresonance of the right side of the chest. The pulse was very feeble and rapid. The blood pressure at this time was 80 systolic and 50 diastolic. The abdomen was soft and tympanitic and showed no unusual changes. Roentgen examination of the chest showed a marked elevation of the diaphragm, displacement of the heart to the left and a patchy infiltration of the lower lobe of the left lung. The observations were characteristic of massive collapse of the lung on the left side.

The patient was in a critical condition for three days, requiring almost continuous administration of oxygen. Then the general condition seemed to improve, the cyanosis lessened and the dyspnea was relieved. The pulse rate continued high, however, and the temperature rose to a higher level. Physical signs in the chest, verified by roentgen examination, denoted an increasing mobility of the left side of the diaphragm, a return of the heart to the right, and also bronchopneumonia on the right side. The latter progressed until it involved the major portion of the lower lobes of both lungs. The temperature reached a maximum of 103.2 F. on the tenth day and began to subside. The leukocytes increased to a maximum of 21,000, with 92 per cent polymorphonuclear elements. The non-protein nitrogen rose to 68 mg. per hundred cubic centimeters. The sputum remained persistently negative for acid-fast organisms, streptococci being present in numbers. Several blood cultures were reported negative. The urine continued to show large quantities of albumin, casts and red and white cells.

On the tenth day following onset of the pneumonia, a sharp rise again occurred in the temperature curve, and the leukocytes rose to 31,400. It was thought that this might be indicative of the formation of an abscess of the lungs, empyema or a general dissemination of the tuberculosis from its focus in the urinary tract. Serial x-ray films of the lungs showed moderate resolution of the pneumonic process in the right lung, but little change on the left side. No pleural exudate was noted.

hands and feet. There was evidence of moderate muscle atrophy in both legs and arms. The deep reflexes were abolished in the legs. Those in the arms were still present, but responded weakly. The abdominal reflexes were not elicited. The cremasteric reflexes were present and active. Babinski's sign was negative bilaterally. Sensation to touch was impaired 2 per cent over the lower legs and the hands. Pain and temperature were unimpaired. Deep pressure to the calves caused considerable pain. The vibratory sense was lost over the feet and tibiae.

Laboratory Data.—On September 1, the specific gravity of the urine was 1.018; the urine was lemon-colored and cloudy. The albumin test gave a 3 plus reaction. The guaiac test gave positive results. The test for sugar was negative. The urine contained many coarsely granular casts and red and white blood cells. On September 1, the phenolsulphonphthalein test showed an excretion of 54 per cent in two hours; on September 5, an excretion of 57 per cent in two hours. Acid-fast bacilli were found in several twenty-four hour specimens of urine. Positive cultures of the tubercle bacilli were obtained from the urine coming from the right kidney during ureteral catheterization.

Examination of the blood showed: red cells, 5,200,000 per cubic millimeter; hemoglobin, 15.3 Gm. per hundred cubic centimeters; white cells, 10,800; differential count: polymorphonuclear neutrophils, 71 per cent; polymorphonuclear eosinophils, 1 per cent; small monocytes, 25 per cent; large monocytes, 3 per cent. The patient's blood belonged to type 4. The Wassermann reaction was negative according to the Kolmer and Kahn technic. The chemical analysis of the blood showed: nonprotein nitrogen, 40 mg., urea, 17 mg. and sugar, 91 mg. per hundred cubic centimeters.

Macroscopic examination of the feces showed no undigested food particles, blood or pus. Microscopic examination revealed no red or white cells, ova or parasites. The guaiac test gave negative results. Several specimens of stools and urine were negative for lead. The stools were persistently negative for acid-fast organisms.

The spinal fluid was clear. The globulin reaction was negative. The spinal fluid contained 3 cells, with a pressure of 16 mm. of mercury. The Wassermann reaction was negative. The spinal fluid contained 59 mg. of sugar per hundred cubic centimeters. The Lange test gave a reaction of 0000112210; the mastic test, 2332210000. The test for lead gave negative results.

Röntgen Reports.—The stomach was empty on the nine hour examination. There was some barium sulphate collected in the terminal ileum and some traces in the cecum and the ascending colon. An enema of barium sulphate showed the colon to be well filled throughout and normal in contour. There was considerable redundancy of the sigmoid portion.

The upper left central incisor tooth had an extensive area of caries in the crown. The upper right central incisor and cuspid were both carious. The lower left first molar was devitalized. There was a diffuse area of lessened density involving the apices of the upper left cuspid and first bicuspid.

There were several small shadows of increased density in the region of the right kidney. A pyelogram showed the upper calyx of the right kidney to be well filled and normal in outline. The middle calyx was large and irregular in outline. The left kidney was considered normal.

No pathologic changes were noted in the cervical spine.

Diagnoses.—The following diagnoses were made: renal tuberculosis of the right kidney; tuberculous epididymitis; peripheral neuritis; oral sepsis—pyorrhea, devitalized teeth and periapical rarefaction—chronic tonsillitis; chronic otitis media.

stripped readily, leaving a smooth, unscarred, cortical surface. On section, the cortex ranged from 5 to 10 mm. in thickness. Dots and striae were readily made out. The pelvis was of usual size and was lined by smooth, intact epithelium. There was no evidence of tuberculosis.

COMMENT

When the patient was admitted to the hospital, the primary problem obviously was to evaluate the cause and extent of his paralysis. It was judged to be due to peripheral neuritis because of its distribution and its characterization by the loss of motor function, sensory changes and reflex signs. The etiologic agent was not so manifest. Four main causes were considered.

1. Lead was favored principally because of the patient's contact with white lead over a period of six years and the marked clinical similarity to lead neuritis with its marked motor and minor sensory manifestations. However, there was no evidence of lead absorption or intoxication and no excretion of lead in the urine or stools and none was present in the spinal fluid or the blood.

2. Tuberculosis as a cause of peripheral neuritis is rare, only a few cases having been reported. Crouzon and his associates¹ reported a case. Oppenheim² described a case of tuberculous myelitis producing symptoms similar to those in the case reported. Tuberculosis could not be definitely ruled out, except for its rarity and its more common association as a predisposing rather than a causative agent.

3. The pneumonia preceding the onset of the symptoms was considered as a possible cause because the infectious diseases, notably diphtheria, are known to produce polyneuritis.

4. The focal infection about the teeth and tonsils was considered as a possible cause, but was less likely than the foregoing infection.

The patient's exposure to lead in the past was considered to have given him a predisposition to polyneuritis, and it was probably precipitated by secondary infections as seen in the tonsils and teeth, supplemented by the tuberculosis. As the patient had harbored the tuberculous kidney for two years, it was decided to clear up all focal infection prior to a nephrectomy, and to this end dental extractions and tonsillec-tomy were performed, the latter being followed by the sequence of complications already described.

The occurrence of massive collapse of the lung following tonsillec-tomy is the first complication that I found reported in the literature.

1. Crouzon, O.; Chavony, J. A.; Bertraud, I., and Froument: Tuberculous Polyneuritis, *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:464 (March 28) 1924.

2. Oppenheim: *Text Book of Nervous Diseases*, London, T. Foulis, 1911.

Meanwhile notable changes were occurring in the neurologic condition. The patient noted that he could use his arms and hands with increasing ease, and he regained the use of his legs to a slight extent, being able to lift his knees from the bed and wriggle his toes.

Neurologic examination at this time showed a definite muscular hypertonus but generalized extensor weakness, the flexor reflexes showing the greater return of function. The grips were definitely present, but could not be reliably recorded on the dynamometer. The patient was able to move the legs, flex the ankles and move the toes. There was no stiffness of the neck. The deep tendon reflexes were very much diminished generally. The biceps and triceps reflexes were obtained but the knee and ankle jerks could not be elicited even with the reinforcement that he was able to give. Pathologic signs in the toes or ankle clonus was not present. The cremasteric reflexes were very brisk. The lower abdominal reflexes could be elicited. There was a definite obtundity of all the sensory receptors, most marked in the lower extremities below the knees. Deep nerve tenderness was present to a moderate degree.

From this time on the course assumed a toxic character. The fever became septic, and the patient manifested progressive emaciation and toxicity. The breath became foul, and x-ray films of the chest revealed observations indicative of an abscess of the lungs. X-ray films of the chest taken after the intratracheal administration of iodized poppy seed oil, 40 per cent, did not localize the abscess satisfactorily. Medical treatment failed to modify the downward course, and thoracotomy was done in an effort to drain the abscess surgically. The patient did not survive the operation.

Autopsy.—Partial postmortem examination was done. The observations were as follows:

The body was that of an emaciated young man, 160 cm. in length. The skeleton was heavy, but there was no subcutaneous fat. The head was of the usual size and shape. The chest was long and deep, and the right side was more prominent than the left. The back showed no curvature. There was a recent surgical wound on the left where portions of several ribs had been resected, and the wound was gaping. There were no anomalies or deformities of importance. The skin was unusually pale. The hair of the head was dark brown. Rigor mortis was not present. There was no postmortem lividity. There was no discharge from the facial orifices.

On exploration through the wound, the left lung was found firmly adherent to the wall of the chest. This was freed with considerable difficulty, and the left lung was brought out through the wound. It weighed 600 Gm. There was a round operative wound 2 cm. in diameter and 6 cm. in depth. Both upper and lower lobes were considerably increased in density, and on section there was a large abscess cavity in each lobe. The cavity in the upper lobe was irregular but approximately 6 cm. in diameter. The lumen was partially filled with foul-smelling, grayish-brown, purulent material. The abscess in the lower lobe was 5 cm. in diameter and contained the same foul-smelling, purulent material. The tissue immediately about the abscesses was firm and grayish yellow.

The heart weighed 240 Gm. The chambers were practically empty. The valves were intact throughout. The base of the aorta was smooth and elastic.

The kidneys were removed because of the question of tuberculosis. The right kidney weighed 200 Gm.; the left, 190 Gm. The right kidney showed the calyces and pelvis markedly dilated. The calyces were lined by soft, yellow, caseous, purulent material. The cortex was of the usual thickness and showed normal dots and striae throughout. The left kidney was of the usual size. The capsule

tion of infective material plugging the bronchi and a secondary collapse of the lung, as maintained by Jackson and Lee. This case is no obvious contribution in favor of the later theory of a reflex mechanism involving the bronchoconstrictor and dilator fibers of the vagus. However, one would be inclined to favor Scott's view that massive collapse does not arise from one particular cause, but consists of a chain of events initiated as a primary nerve reflex, causing bilateral partial obstruction in the peripheral system. plus such secondary factors as position, tenacious secretion or infection, which make the obstruction complete on one side in advance of that on the other. A hyperventilation on the opposite side keeps the passages open. Then the air on the occluded side is absorbed in a few hours, and the complete picture develops.

The clearing of the neurologic manifestations in the presence of a continued tuberculous focus and while the patient was subjected to the exceedingly toxic effects of pneumonia was the most unusual aspect of the case. This would seem to mitigate against tuberculosis as a causative factor, because it was still present; against lead because no evidence of lead absorption was found and no deleading process was carried out, and against pneumonia because improvement occurred in the presence of a second pneumonic process. Conversely, it would seem to favor focal infection as the etiologic agent, as improvement occurred following the removal of focal infection. The latter would seem to be the most satisfactory explanation. An interesting speculation arises as to whether a repetition of the massive collapse of the lung would occur if a nephrectomy were performed, a reaction that occurred in a case reported by Scott after subsequent nephrectomies and by Farrar after subsequent laparotomies, the occurrence of which is adduced as supportive evidence in favor of the neurogenic theory of causation, these persons being thought to have a predisposition to massive atelectasis.

SUMMARY

The history and course of a case of peripheral neuritis with paralysis are submitted. The etiology of this case still presents interesting speculation. The interesting features of the case were the clearing up of the paralysis following the removal of focal infection and the occurrence of massive collapse of the lung following tonsillectomy.

The occurrence and diagnosis of this condition are now well known, having been first reported by Pasteur³ in a series of cases following diphtheritic paralysis and in a later series following abdominal operations.⁴ Bradford⁵ then published a series of cases in which this condition followed gunshot wounds of the chest. Scrimger⁶ reported the first cases in the American literature. Since then numbers of cases have been reported by Scott,⁷ Elliot and Dingley,⁸ Leopold,⁹ Lund and Ritvo,¹⁰ Jackson and Lee,¹¹ Smith and Davidson¹² and others.

The most excellent reviews of the subject have been published by Scott⁷ and Leopold.¹³ The preponderance of cases of massive collapse of the lung occur after abdominal operations and wounds of the chest. A few cases have been reported in which this complication occurred following nephrectomy and thyroidectomy. Regan¹⁴ reported a case in which collapse occurred during the course of anterior poliomyelitis, and Kletz¹⁵ reported one in which collapse occurred during the course of meningitis.

The mechanism of this phenomena is still in the controversial stage. The case reported would seem to support the view that there are a series of factors at work rather than any single one of those particularly advocated. The occurrence of the condition in a person already manifesting paralysis would indicate a possible primary involvement of the diaphragm and a secondary collapse of the lung, which view was originally held by Pasteur. The occurrence following tonsillectomy and the development of the infective complications point to an aspira-

3. Pasteur, William: *Am. J. M. Sc.* **100**:242, 1890.

4. Pasteur, William: *Brit. J. Surg.* **1**:587, 1914.

5. Bradford, John R.: *Massive Collapse of the Lung*, *Quart. J. Med.* **12**:127, 1919.

6. Scrimger, F. A. C.: *Surg. Gynec. Obst.* **32**:486 (June) 1921.

7. Scott, W. J. M.: *Postoperative Massive Collapse of the Lung*, *Arch. Surg.* **10**:73 (Jan.) 1925.

8. Elliot, T. R., and Dingley, L. A.: *Massive Collapse of Lung Following Abdominal Operations*, *Lancet* **1**:1305, 1914.

9. Leopold, S. S.: *Post-Operative Massive Pulmonary Atelectasis and Drowned Lung*, *Am. J. M. Sc.* **167**:421, 1924.

10. Lund, C. C., and Ritvo, Max: *Post-Operative Massive Collapse of the Lung*, *Boston M. & S. J.* **190**:1103, 1924.

11. Jackson, C., and Lee, W. D.: *Acute Massive Collapse of the Lungs*, *Ann. Surg.* **82**:364, 1925.

12. Smith, F. J., and Davidson, E. C.: *Post-Operative Pulmonary Atelectasis*, *J. Michigan M. Soc.* **26**:295, 1927.

13. Leopold, S. S.: *Massive Collapse of the Lung: Bedside Diagnosis* (Blumer), Philadelphia, W. B. Saunders' Company, 1928.

14. Regan, J. C.: *Massive Collapse of the Lung in Acute Poliomyelitis*, *Lancet* **2**:1222, 1924.

15. Kletz, N.: *Massive Collapse of the Lung Complicating Acute Meningitis*, *Lancet* **1**:179, 1927.

comatous change and which do not usually produce true intragastric polyps, have sometimes been included.

The accumulated data on these two groups of cases will be presented separately, since the diagnostic study has been more complete in our personal series, but so far as the investigations made and recorded in the two groups have corresponded, it will be noted that the observations have been quite similar. Each of the thirty-two cases showed carcinoma of at least one intragastric polyp, and evidence will be adduced to indicate that the primary lesions were benign adenomatous polyps.

INCIDENCE

The incidence of polyp of the stomach, whether benign or malignant, is difficult to determine at the present time. This is due largely to the fact that until recently preoperative clinical diagnosis was impossible; also, at operation, unless specially considered, a polyp is easily overlooked, and at autopsy, if a secondary malignant process has occurred, it may be so extensive as to obscure the nature of the primary lesion. Today; however, with improvement in roentgenologic technic, the diagnosis may be made quite early, even before symptoms or any of the complications have occurred, and consequently it may be expected that in the future the incidence of the disease may be more accurately indicated.

That gastric polyp is not rare is shown by the fact that two of us (Eliason and Wright¹), in 1925, were able to collect 610 cases of primarily benign gastric tumors, including 560 from the literature and 50 from the surgical and autopsy records of this and the Philadelphia General Hospitals (8,000 autopsy records reviewed). Of this total number, it is impossible to say how many patients had pedunculated tumors, but of our 50 cases, 35, or 70 per cent, showed polyps. Since that time, 6 other cases of polyp have been observed. Of this total of 41 cases of gastric polyp, including 9 that have been operated on by one of us (E. L. E.), 23 supplied specimens that were subjected to careful microscopic study, and of this number 8, or 35 per cent, showed carcinomatous change.

In referring to polyps of the entire digestive tract, and not merely to those of the stomach, Wechselman² stated that from 50 to 60 per cent become malignant, and Doering³ gave the percentage figure as 46. Muehlengracht⁴ agreed that one half or more of intestinal polyps under-

1. Eliason, E. L., and Wright, V. W. M.: Benign Tumors of the Stomach, *Surg. Gynec. Obst.* **41**:461 (Oct.) 1925.

2. Wechselman, L.: Polyp und Carcinom im Magen-Darmkanal, *Beitr. z. klin. Chir.* **70**:855, 1910.

3. Doering, H.: Die Polyposis intestini und ihre Beziehung zur carcinomatösen Degeneration, *Arch. f. klin. Chir.* **83**:194, 1907.

4. Muehlengracht, E.: Ueber die Gastritis polyposa, *Virchows Arch. f. path. Anat.* **214**:438, 1913.

CARCINOMATOUS DEGENERATION OF POLYP OF THE STOMACH

REPORT OF EIGHT PERSONAL CASES WITH A REVIEW OF TWENTY-FOUR RECORDED BY OTHERS *

T. GRIER MILLER, M.D.

E. L. ELIASON, M.D.

AND

V. W. M. WRIGHT, M.D.

PHILADELPHIA

Polyp of the stomach is of clinical importance chiefly because of its tendency to undergo malignant degeneration; it is important also because of its tendency, whether benign or malignant, to give rise to hemorrhage and to pyloric obstruction. In a group of eight cases of carcinomatous gastric polyp that we have observed during the past ten years, three patients had experienced gastric hemorrhage of such a degree as to lead to a preliminary diagnosis of primary anemia, and all but one had developed pyloric stenosis. These three phenomena—malignancy, hemorrhage and obstruction—may be looked on as the important consequences of gastric polyp, but it is to carcinomatous transformation particularly that we wish to direct attention at this time.

Under the heading of benign polyp of the stomach is included, strictly speaking, all the nonmalignant intragastric pedunculated tumors; but, since the myoma, the fibroma, the angioma, the lipoma and the myxoma are only rarely pedunculated and have not been encountered in our group of cases, they are excluded from this report. Reference is made, therefore, only to those of an adenomatous nature, which, because of their epithelial structure, when malignant show carcinomatous change.

In addition to our personal series of eight cases of carcinomatous gastric polyp, a group of twenty-four has been collected from the literature. To one making a hurried review, it may seem that many more cases have been reported. This is due to the fact that certain authors have not differentiated clearly between polyps of the stomach and those of other portions of the digestive tract; furthermore, some of them have not distinguished between polyps that were themselves malignant and polyps associated with malignancy elsewhere in the stomach. Also, interstitial benign tumors, such as myoma and fibroma, which undergo sar-

* Submitted for publication, April 3, 1930.

* From the Gastro-Intestinal Section of the Medical Clinic, and the Surgical Service C, of the Hospital of the University of Pennsylvania.

he had suffered for a period of three weeks. Eighteen months previously, as a soldier, he had been studied in the United States Base Hospital at Camp Meade on the service of Dr. Nellis B. Foster, and at that time his disease had been diagnosed as primary pernicious anemia (red blood cells, 1,000,000; hemoglobin, 40 per cent). No gastric analysis and no examination of the stool were reported. Five transfusions of blood, 300 cc. each, were given. He made a good symptomatic recovery, and subsequent blood studies were normal.

On examination in November, 1919, a hard, tender and movable mass about the size of a lemon was felt under the right costal margin just to the right of the xiphoid. Peristaltic waves were visible, and as certain ones reached the median line the stethoscope revealed a distinct squirting sound. A small, firm, freely movable gland just above the inner end of the left clavicle was palpable. Blood counts and the hemoglobin estimation were within normal limits. Repeated gastric analyses showed achlorhydria. The feces showed a trace of occult blood on one occasion, the examinations of other stools for blood being negative. The Wassermann reaction was negative.

Roentgenologic study showed an almost complete gastric residue six hours after a barium sulphate meal, marked hyperperistalsis with deep segmenting waves, the waves coursing along the curvatures without interference, and just above the greater curvature in its most dependent part a large, clear area about the size of a silver dollar. The serial exposures showed a constant vacuole defect strongly suggesting duodenal ulcer. It was concluded that pyloric obstruction was present, probably of duodenal origin, and that the gastric defect was probably due to a papilloma, possibly malignant.

At operation by Dr. John B. Deaver, a gastrotomy revealed a rounded, polypoid mass about the size of a walnut attached by a pedicle to the mucous membrane along the greater curvature. The muscle coats did not seem to be involved. The mass that had been palpated at the bedside was found to be a secondary lesion attached to the edge of the liver. Dense adhesions involved the gallbladder and duodenal bulb and explained the duodenal deformity noted on roentgenologic study. Glandular metastatic lesions were also observed.

The intragastric mass was excised and is described completely, with illustrations, in the original report of this case. It showed a malignant papillomatous portion, a simplex portion and a scirrhus portion. Some ulceration was noted over the free surface of the tumor.

The patient died about three weeks after the operation, and autopsy was not obtained.

CASE 2.—E. K.,¹¹ a man, aged 45, had been without symptoms of any sort until about three months before his admission to the hospital on April 30, 1923, when he first became aware of epigastric discomfort, and later of a gnawing epigastric pain before meals. Ingestion of the softer foods, especially milk, gave relief, whereas the coarser foods increased the pain. On two occasions the pain had been very severe. He had lost 40 pounds (18.1 Kg.), his best weight being 220 pounds (99.7 Kg.). Blood-streaked material had been vomited twice. He had been in the habit of taking whisky before each meal. He gave a history of stone in the bladder ten years previously.

11. Reported previously as case 1 by Eliason, E. L.; Pendergrass, E. P., and Wright, V. W. M.: The Roentgenological Diagnosis of Pedunculated Growths and Gastric Mucosa Prolapsing Through the Pylorus, *Am. J. Roentgenol.* **15**:295 (April) 1926.

goes malignant degeneration, but insisted that such change in the lesions located in the stomach is rare. Mills⁵ found evidence of malignancy in 20 per cent of twenty collected cases of gastric polyp, and Brunn and Pearl⁶ in 12 per cent of their eighty-four cases, while Balfour and Henderson⁷ found such degenerative change in only 3.5 per cent. Stewart,⁸ in forty-seven cases of gastric polyp encountered in 11,000 necropsies, discovered associated carcinoma in thirteen, but in only three (6.4 per cent) could it be determined that the malignant process had originated in a polyp. In defense of our somewhat higher percentage figure, it may be stated that sometimes only one of several polyps in a single case showed the malignant change, and that, because of our interest in the exact diagnosis, an extensive search of many sections was made in each instance.

The significance of gastric polyp may be appreciated if the number undergoing malignant change is considered in relation to the total number of cases of gastric carcinoma. For instance, our 8 cases have been found in a series of about 200 operations for cancer of the stomach, thus constituting approximately 4 per cent of the group. Stewart⁸ had 13 cases of gastric carcinoma that were probably secondary to adenomatous polyp, all at least being associated with such polyps, in 263 cases of gastric cancer, about 5 per cent. This approximates the percentage of cases of carcinoma occurring on an ulcer basis. Thus, as Hurst⁹ has suggested, adenomatous polyp, like ulcer and chronic gastritis, may be looked on as a precursor of carcinoma of the stomach.

The relatively large number of our malignant cases, encountered in a single hospital within a decade, in comparison with the number that we have been able to collect from the literature, suggests that insufficient attention has been given to this subgroup of gastric cancer and to this important and frequent complication of gastric polyp.

PERSONAL CASES

CASE 1.—F. A. D.,¹⁰ an American, a white man, aged 31, was admitted to the hospital on Nov. 12, 1919, because of epigastric pain and anorexia from which

5. Mills, G. P.: Multiple Polypi of the Stomach (Gastritis Polyposa): With the Report of a Case, *Brit. J. Surg.* **10**:226 (Oct.) 1922.

6. Brunn, H., and Pearl, F.: Diffuse Gastric Polyposis-Adenopapillomatosis Gastrica, *Surg. Gynec. Obst.* **43**:559 (Nov.) 1926.

7. Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Stomach, *Ann. Surg.* **85**:354 (March) 1927.

8. Stewart, M. J.: The Relation of Malignant Disease to Benign Tumours of the Intestinal Tract, *Brit. M. J.* **2**:567 (Sept. 28) 1929.

9. Hurst, A. F.: Precursors of Carcinoma of the Stomach, *Lancet* **2**:1023 (Nov. 16) 1929.

10. Reported in full by Miller, T. G.: Polypoid Carcinoma of the Stomach, *J. A. M. A.* **76**:229 (Jan. 22) 1921.

At this time roentgenologic study showed no gastric residue, normal peristalsis, slightly increased motility and a constant vacant area in the antrum pylori (fig. 2). A diagnosis of papilloma or nodular carcinoma in the pyloric region was made.

Operation by one of us (E. L. E.) on Feb. 13, 1924, revealed a small lump on the posterior wall of the stomach, which could be pushed along the lumen of the organ toward the pylorus. Gastrotomy was then performed, and the affected area of the posterior wall was pushed out through the opening, displaying three polyps,



Fig. 1 (case 2).—Serial roentgenograms, viewed from behind, showing the constant circular defect of the first portion of the duodenum. Roentgenologic diagnosis: duodenal ulcer or adhesions (1923).

one the size of a cherry and the other two much smaller.¹³ Each had a separate pedicle. The polyps were excised. The patient made a good recovery, except for a slight attack of bronchitis, and was discharged a month later.

13. See the illustrations included in the original article.

Physical examination revealed only some tenderness in the epigastrium, the edge of the liver palpable, dental caries and ragged tonsils. His blood pressure was 152 systolic and 100 diastolic. The red blood cells numbered 4,300,000, and the leukocytes, 10,000. The hemoglobin percentage was 81. Urinalysis gave negative results. The feces showed occult blood. The Wassermann reaction of the blood was negative. Fractional gastric analysis revealed achlorhydria; this was confirmed by three subsequent analyses.

On three occasions, while under observation, he had attacks of severe epigastric pain, one of these attacks requiring morphine for relief. Although roentgenologic renal study revealed a stone in the pelvis of the right kidney, the location of the pain was such as to suggest that it was gastric rather than renal in origin.

Roentgenologic study of the gastro-intestinal tract showed moderate gastric residue, intermittent hyperperistalsis, hypermotility at times (usually less than commensurate with the peristalsis), pyloric spasm or obstruction and a defect of the duodenal bulb, producing almost complete obliteration of this portion of the duodenum. The diagnosis of the roentgenologist was duodenal ulcer or adhesions.

On May 16, an exploratory laparotomy by one of us (E. L. E.) revealed only a gastric polyp and some duodenal adhesions. A gastrotomy was performed, and the polyp, which was found attached to the posterior wall of the stomach near the pylorus, was excised. The patient died on the following day. Autopsy disclosed an additional and extensive lesion high up on the posterior aspect of the fundus of the stomach, which had not been observed at operation, and which proved to be carcinomatous. Microscopic study of the polyp, removed at operation, showed it to be a papilloma that also was undergoing carcinomatous change.

Review of the roentgenologic films in this case disclosed a circular central defect in the duodenal bulb (fig. 1), which was due undoubtedly to protrusion of the polyp through the pylorus, since autopsy showed the pylorus to be wide open, and no other explanation for such a defect was suggested. Since that time such defects have led to a correct diagnosis, as subsequent cases will illustrate.

¹ CASE 3.—G. L.,¹² a Negro, a day laborer, at the age of 39 was first admitted to the medical service of the Presbyterian Hospital, of Philadelphia, on Dec. 26, 1917, stating that for two months he had been having gnawing pains in the region of the stomach. They usually appeared soon after eating, but sometimes several hours after a meal. Heavy foods especially seemed to produce the pains. He had lost some weight, but had not vomited. He showed considerable emaciation, and the abdomen was distended, tympanitic and without palpable masses.

A tentative diagnosis of carcinoma of the stomach was made, and operation advised. This was refused, but finally the patient was discharged greatly improved. In 1920, he was readmitted to the Presbyterian Hospital and operated on, the stomach and duodenum being reported as normal. At that operation his appendix was removed, and some adhesions about the gallbladder were freed. Subsequently he was observed in our outpatient medical dispensary, and repeated gastric analyses over a three year period constantly showed achlorhydria. Repeated Wassermann tests gave negative results.

He was admitted to our medical wards on Jan. 25, 1924, still complaining of abdominal pains, now of an aching character, more or less constant and increased by activity. He had lost from 20 to 30 pounds (9 to 13.6 Kg.). Another fractional gastric analysis showed achlorhydria. Blood studies, including another Wassermann test, gave negative results.

12. This case also was reported previously, as case 2, by Eliason, E. L.: Pendergrass, E. P., and Wright, V. W. M.: *Am. J. Roentgenol* 15:295 (April) 1926.

suggesting only adhesions. A repetition of this examination two weeks later gave the same results.

The large polyp removed from the stomach in 1924 proved to be an adenoma undergoing malignant change.

CASE 4.—J. M., a man, an interior decorator, aged 45, became a private patient of one of us (T. G. M.) on Sept. 27, 1927, and stated that he had been without

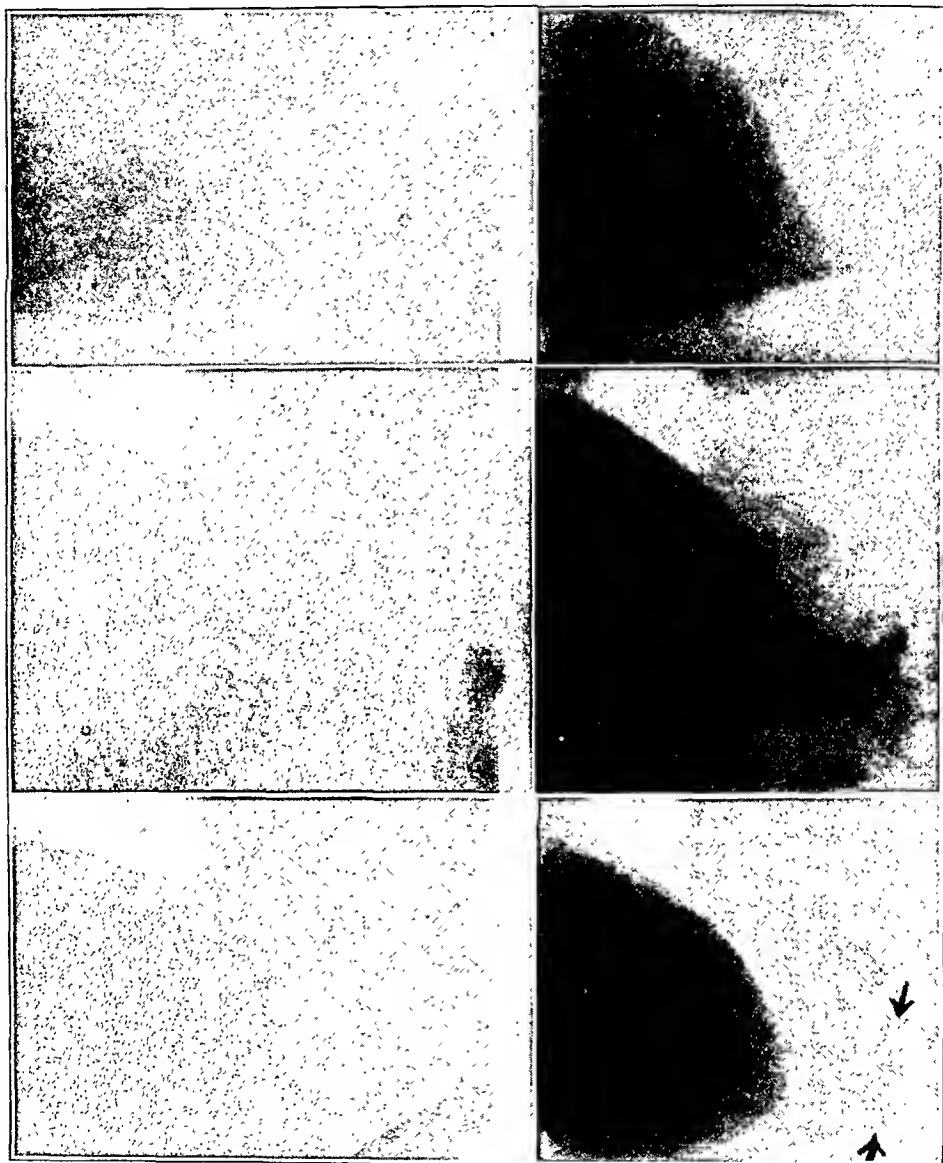


Fig. 3 (case 4).—Serial roentgenograms, viewed from behind, showing a large defect in the pyloric region and the lower third of the stomach; also a large basal deformity of the duodenal cap. Roentgenologic diagnosis: probable carcinoma (1927).

symptoms of any kind until three weeks previously. At that time, after a heavy meal, he had become nauseated and had vomited. Subsequently he had had almost constant epigastric distress with eructations, a sense of abdominal distention and, irregularly, nausea and vomiting. He had not had any severe pain. He had lost

Three months later he had a recurrence of his abdominal pain which has persisted since that time. On Feb. 26, 1925, he was readmitted to the medical wards for roentgenologic study, which showed no residue, good peristalsis and motility and defects suggestive of perigastric adhesions. No evidence of a recurrence of the polyps was made out.

Since then he has been under observation in the gastro-intestinal clinic. His pain has varied, usually being less severe, and his weight has increased. He has

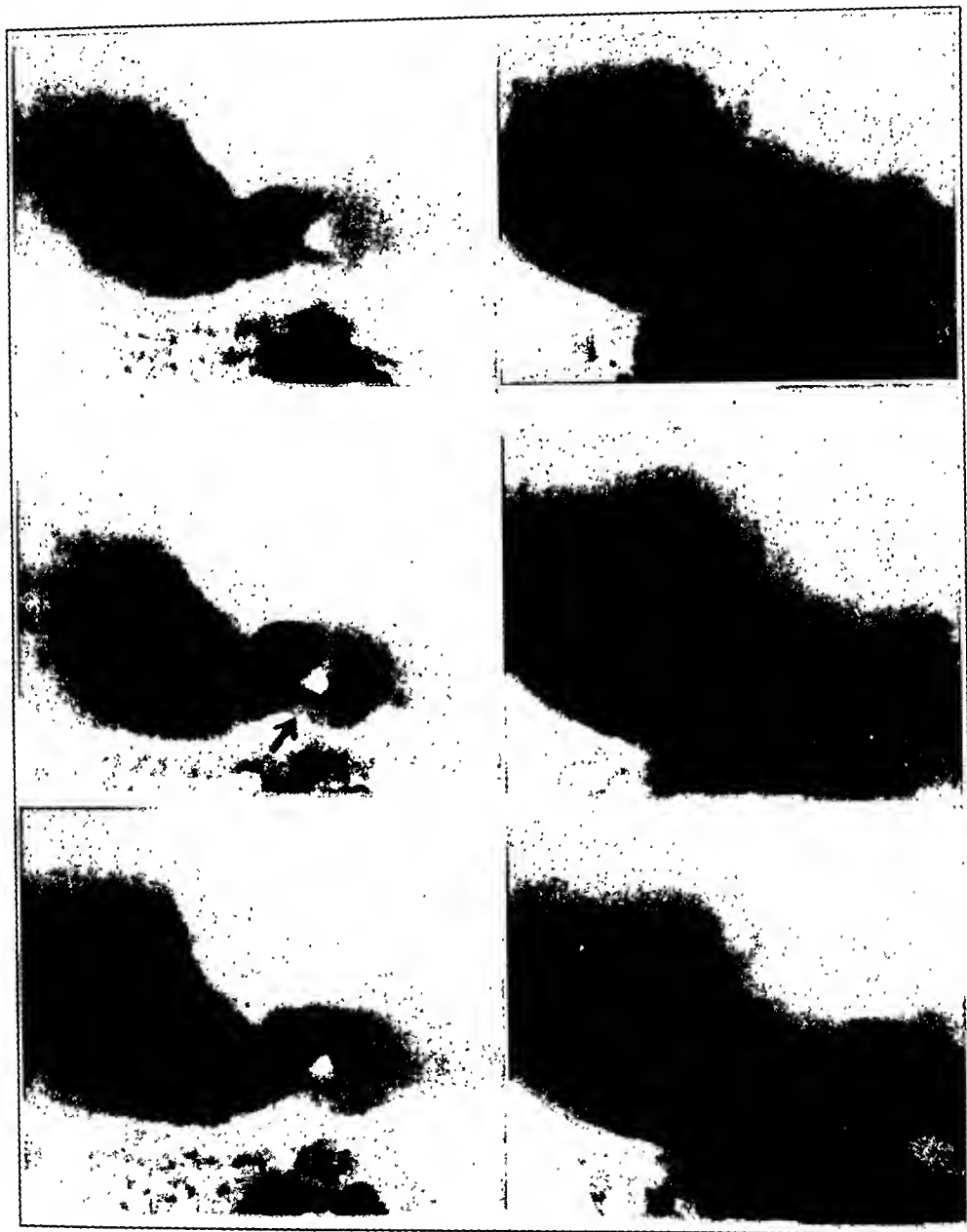


Fig. 2 (case 3).—Serial roentgenograms, viewed from behind, showing the constant area of decreased density in the pyloric antrum. Roentgenologic diagnosis: papilloma or nodular carcinoma (1924).

been able to resume work as a night watchman. Two more fractional gastric analyses have showed the same achlorhydria. Another gastro-intestinal roentgen study on Dec. 1, 1926, showed no residue, normal peristalsis in the distal third of the stomach, increased motility and some irregularity in the outline of the stomach

At operation, on Oct. 26, 1927, by one of us (E. L. E.), the pylorus was found to be quite hard and suggestive of carcinoma. The induration involved the entire circumference of the wall of the stomach and extended upward for 3 inches (7.6 cm.) beyond the pylorus. A nodular piece of tissue was palpated in the duodenal cap, and it was slipped back into the stomach without opening the latter organ. A few small nodules in the lesser omentum were noted. A subtotal gastrectomy with the Polya type of anastomosis was performed. Although the

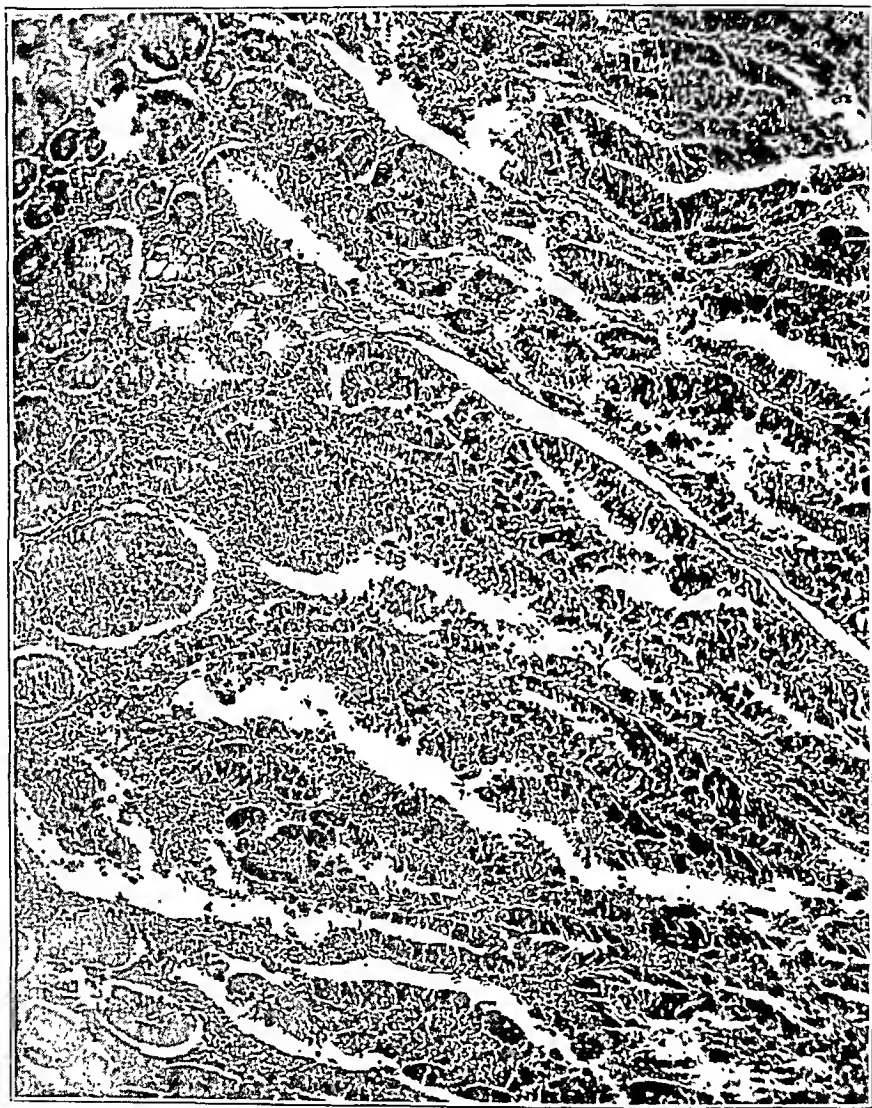


Fig. 5 (case 4).—Photomicrograph, showing adenocarcinomatous changes in the polyp.

immediate convalescence was somewhat stormy, the patient left the hospital on November 15, and a month later was gaining weight, had a good appetite and complained only of diarrhea when he did not keep to a strictly starchy diet. He returned to his work, felt as well as ever and in May, 1928, was back to his usual weight.

A second roentgen study in the following month showed no filling defects, no gastric residue, a stomach of the size and shape of an orange and an occasional

15 pounds (6.8 Kg.) during the three weeks. His past medical history was negative. His mother had died of carcinoma of the breast. He had been under considerable strain because of business difficulties and because of the illness of his wife, who had exophthalmic goiter. Two children were in good health.

Physical examination revealed only some carious teeth with pyorrhea, evidence of the loss of weight and a little soreness in the epigastrium. Urinalysis and the usual examinations of the blood gave negative results. The Wassermann reaction



Fig. 4 (case 4).—Photograph of the specimen removed at operation, showing the thickened gastric wall and polyp on the posterior wall near the pylorus.

of the blood was negative. A gastric analysis indicated marked gastric retention and achlorhydria. The blood pressure was 155 systolic and 105 diastolic.

Roentgenologic study showed a complete gastric residue after six hours, no peristalsis and only slight motility on one occasion. A large defect in the pyloric region and the lower third of the stomach and a constant basal deformity of the duodenal cap were noted (fig. 3). The roentgenologist's diagnosis was probable carcinoma of the pyloric end of the stomach, with a syphilitic lesion as a possibility. It was suspected that the duodenal deformity was due to the gastric lesion.

having from three to six bowel movements daily for six years, but was otherwise in good health until about six months previously, when she noted some dizziness on stooping; occasionally she would fall during such attacks. Two months before admission, and following the eating of steamed clams, definite diarrhea developed associated with colicky pain in the abdomen. From that time until her admission she had had from five to twenty movements a day, liquid, gray or yellow, containing considerable mucus. The pain did not persist. Blood was observed in the stools on several occasions, but the amount was not large. The fecal evacuations were particularly frequent immediately after eating. She was not specially weakened by the diarrhea, but when first seen she was 25 pounds (11.3 Kg.) below her average weight. Her appetite was impaired, but there had been no nausea or vomiting.

She had had malaria at the age of 31, and had passed through her menopause at 40 without special symptoms. Her husband had died thirty-five years previously, and her only child, a daughter of 40, was living and in good health. Her habits were excellent.

Physical examination showed her to be fairly well developed and nourished, weighing 116 pounds (52.6 Kg.). No focal infections were found. The abdomen was soft and slightly distended and presented some tenderness to deep pressure over the cecal area and in the upper left quadrant. No other physical abnormalities were discovered.

On October 8, a simple test meal showed no free hydrochloric acid and a total acidity of 25. The amount of gastric contents removed at the end of forty-five minutes was 100 cc. The occult blood test gave positive results. A fractional gastric analysis showed no free hydrochloric acid in any of the specimens, but occult blood was constantly present. The Wassermann reaction of the blood was negative.

Proctoscopic examination showed a small polyp, about one-half the size of an olive, springing from the anterior wall of the rectum about 4 inches (10.16 cm.) above the anus. The surface of this was smooth and of normal color, and did not bleed when touched. Otherwise, the results of the examination were negative. Examination of the feces by Dr. Frank B. Lynch, Jr., showed no parasites or ova, many pieces of undigested vegetable material and a positive occult blood test. Several subsequent examinations of the feces gave similar results. A Gram stain showed an excess of gram-negative organisms.

Gastro-intestinal roentgenologic study showed a marked gastric residue, the stomach being J-shaped and atonic with the greater curvature about 1 inch (2.5 cm.) below the level of the iliac crests. Continual hyperperistalsis was observed, but the waves were not numerous; they moved slowly, and were deep and segmenting. Motility was commensurate. The waves started in the fundus and progressed to the pylorus without interference. The films of the stomach indicated a lesion involving the greater curvature, which was interpreted as probably due to carcinoma (fig. 7). A barium enema study gave negative results.

The patient was admitted to one of the medical wards for study and observation on October 24, but nothing new was noted. Finally, on November 28, surgical exploration of the abdomen by one of us (E. L. E.) disclosed a mass at the junction of the middle and lower thirds of the stomach. It did not seem to be attached to all the coats of the wall of the stomach, since at least the outer coat could be moved over it on all sides, and a large polyp was suspected. A sleeve resection of the stomach without preliminary gastrotomy was performed. The patient made an uneventful recovery from the operation, except for the development of a few pus pockets in the wound, and was discharged on Jan. 9, 1928.

spurt of contents into the jejunum by tonic contraction of the wall of the stomach. During the following February (1929), however, symptoms indicative of gastric obstruction again developed, he lost weight and strength rapidly and died on March 7, presumably of an extensive recurrence of his primary lesion. Autopsy was not obtained.

The specimen removed at operation consisted of the lower third or half of the stomach. Throughout all but the free borders of it, much thickening and

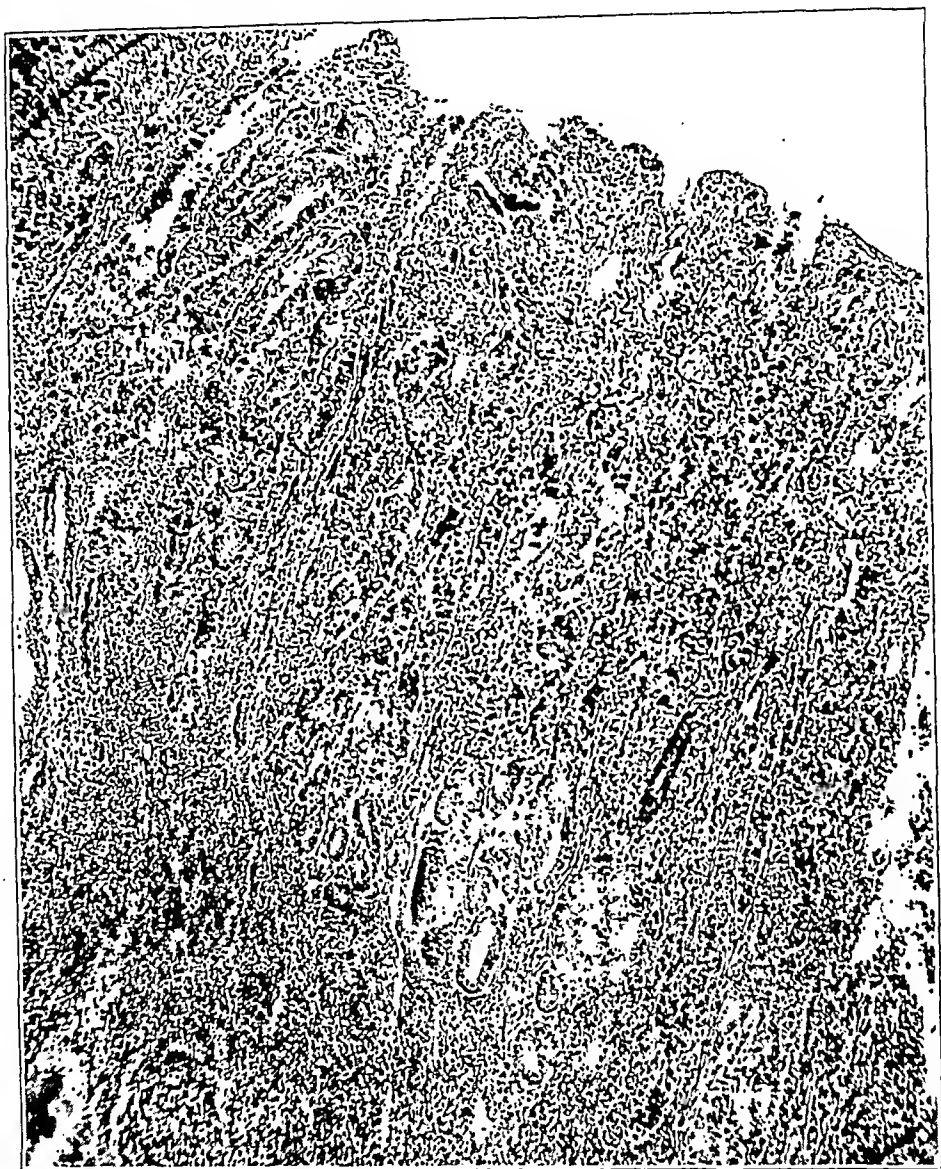


Fig. 6 (case 4).—Photomicrograph from the stomach near the abscess at the base of the polyp, showing adenocarcinoma with marked round cell infiltration.

induration were present, and attached by a pedicle to the posterior wall was a polyp that measured 3.5 cm. in diameter (fig. 4). An abscess was found at the base of the polyp. Microscopic sections showed: (1) adenocarcinoma of the polyp and (2) chronic inflammatory changes in the wall of the stomach, with malignant change in certain areas (figs. 5 and 6).

CASE 5.—A. M., the only woman in our series, aged 61, was admitted to the gastro-intestinal clinic on Oct. 6, 1927, complaining of diarrhea. She had been

quadrant of the abdomen; the liver was enlarged and irregular. Her weight was decreasing. It was believed that an extensive recurrence of cancer had developed.

The specimen removed (fig. 8) showed three polyps on its mucosal surface, each being attached by a separate pedicle. The largest one measured 6 by 3.5 by 3 cm. and each of the others about 1 cm. in diameter. All of the lesions were soft, friable and hemorrhagic. Microscopic sections showed that one was probably a benign adenoma and one an adenocarcinoma, and that one was undergoing early malignant change (figs. 9, 10 and 11).



Fig 8 (case 5) —Photograph of the specimen removed at operation, showing three polyps

CASE 6.—H. C, a fish dealer, aged 47, a private patient of Dr. Alfred Stengel, was admitted to our medical wards on Oct. 19, 1927. He had been in good health until two years previously when, following his wife's death, anorexia and gaseous eructations developed, later, pallor and loss in weight (22 pounds [10 Kg.] in the two years) were noted. Six weeks before admission he had to give up his work on account of weakness, headache, dyspnea, palpitations and paresthesia of the extremities.

On February 14, her weight was only 111 pounds (50.3 Kg.) in spite of the development of peripheral edema, and she was quite weak, but the diarrhea had disappeared. Soon afterward she began to improve in every way, and on March 7, a roentgenologic examination showed only a slight gastric residue and a progression of the peristaltic waves from the fundus to the pylorus with an occasional antiperistaltic wave. It was concluded that the stomach was functioning satisfactorily.

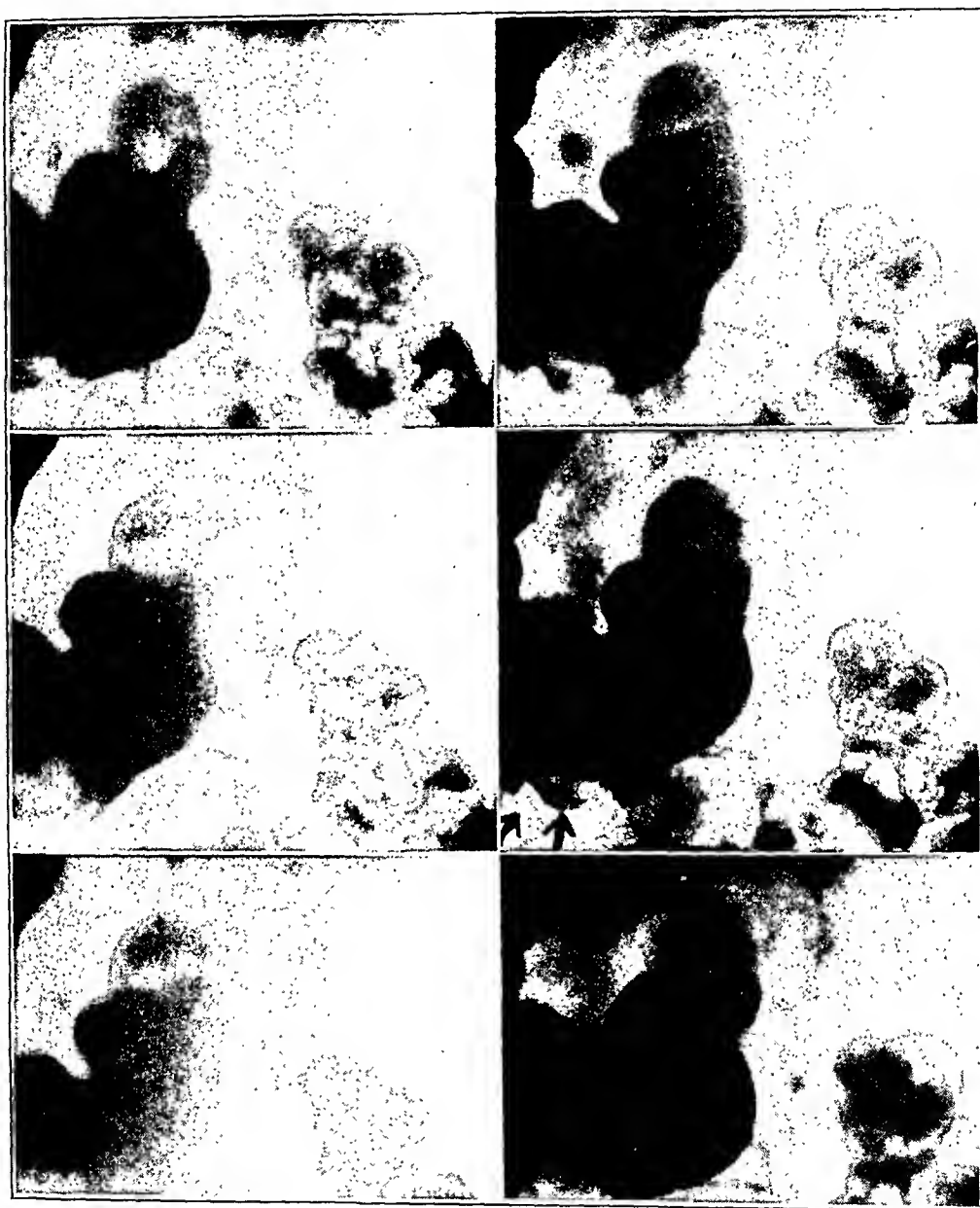


Fig. 7 (case 5).—Serial roentgenograms, viewed from behind, showing a constant defect along the greater curvature of the stomach. Roentgenologic diagnosis: probable carcinoma (1927).

She had gained 7 pounds (3.2 Kg.) by June 5, and on March 5, 1929, weighed 137½ pounds (62.3 Kg.), 21½ pounds (9.8 Kg.) more than before her operation. No edema was present at that time, and she had no complaints except that she was too stout. By November, however, a fixed mass had developed in the left lower

Physical examination showed marked pallor of the skin and mucous membranes, some atrophy of the tongue, a systolic apical heart murmur, a vague epigastric mass, a questionable Ewald gland and some uncertain sensory changes in the legs. The red blood cells numbered 2,800,000 and the leukocytes, 12,200, and the hemoglobin percentage was 30. Nucleated red cells were found. The van den Bergh test gave negative results. The blood platelets numbered 272,000, and the reticulated red blood cells amounted to 3.5 per cent. A blood culture was negative. Fractional gastric analysis, with and without histamine, showed achlorhydria. The feces, on a meat-free diet, were positive for occult blood. The Wassermann reaction of the blood serum was negative.

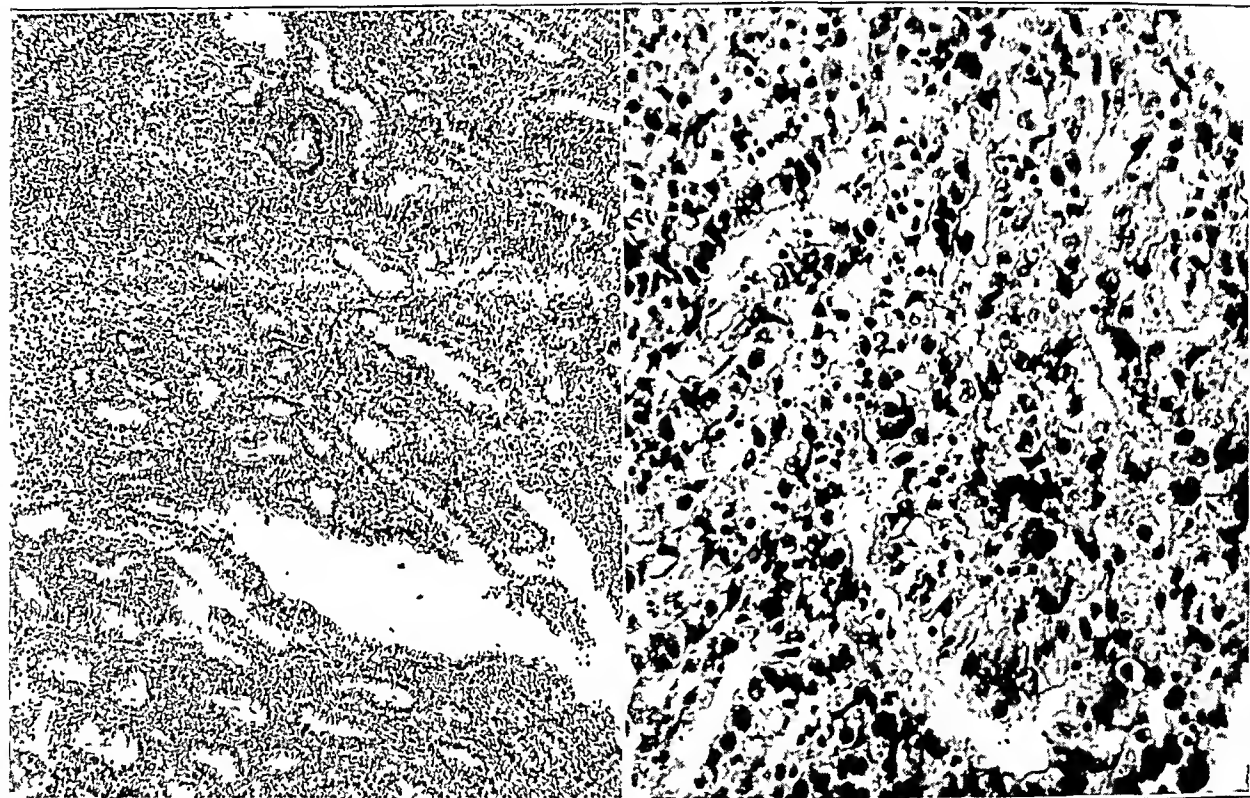


Fig. 11 (case 5).—Low and high power photomicrographs from the intermediate-sized polyp, showing early malignant degeneration.

He had some fever, and a subacute endocarditis was considered. This was later abandoned for a diagnosis of primary pernicious anemia. The possibility of a gastric polyp with malignant change was also suggested.

Roentgenologic investigation of the gastro-intestinal tract showed a marked gastric residue, normal peristalsis and motility and a large filling defect along the greater curvature of the stomach at its middle portion (fig. 12). In spite of the defect, the peristaltic waves progressed to the pylorus without interference. The roentgenologic diagnosis was a large carcinoma or a benign tumor along the greater gastric curvature.

Following two transfusions of blood, 350 cc. each, one of us (E. L. E.), at operation on November 2, found a large cakelike mass in the stomach, apparently having a crater and apparently attached to the posterior wall near the greater

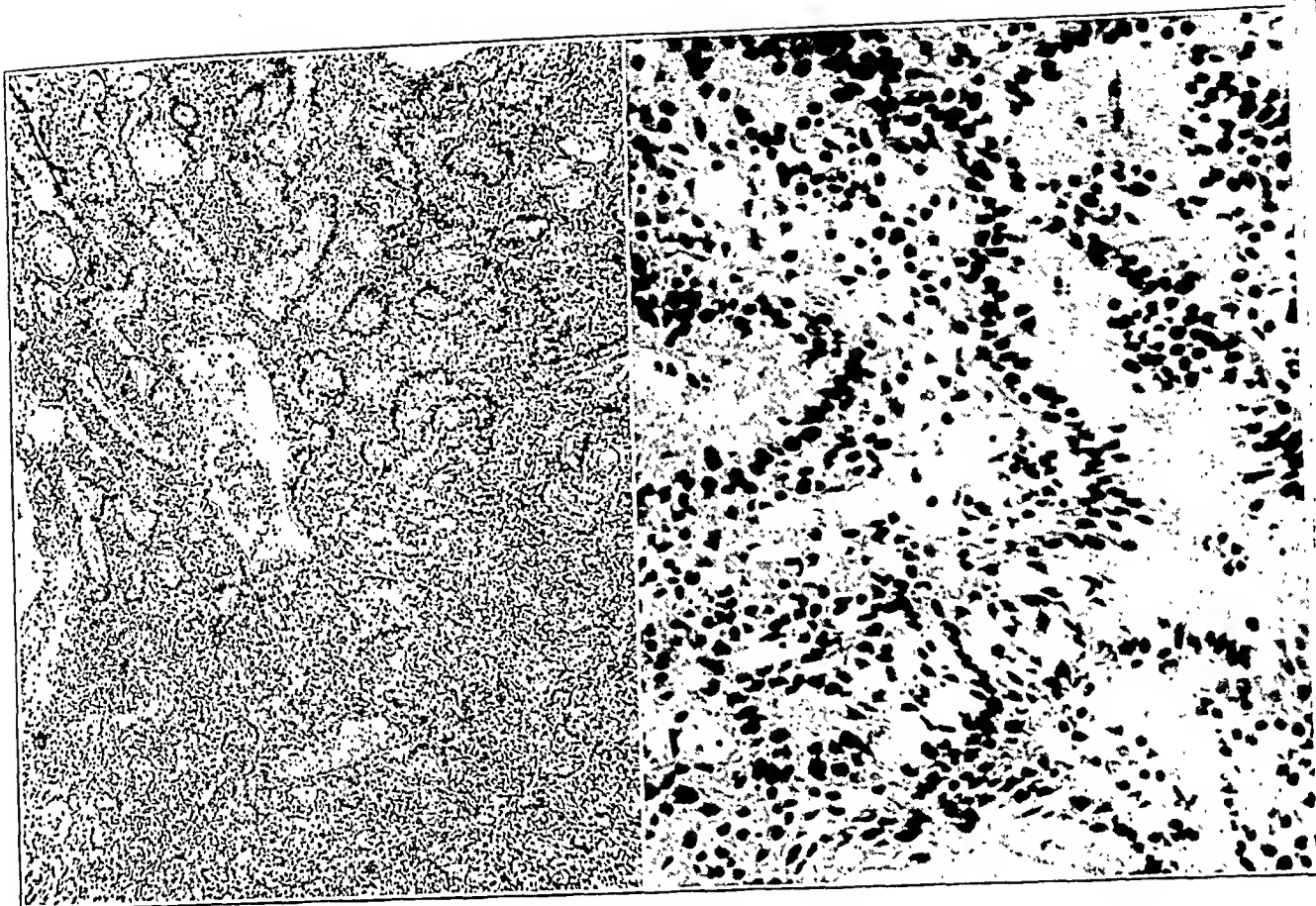


Fig. 9 (case 5).—Low and high power photomicrographs of smallest polyp, showing adenoma, probably benign.

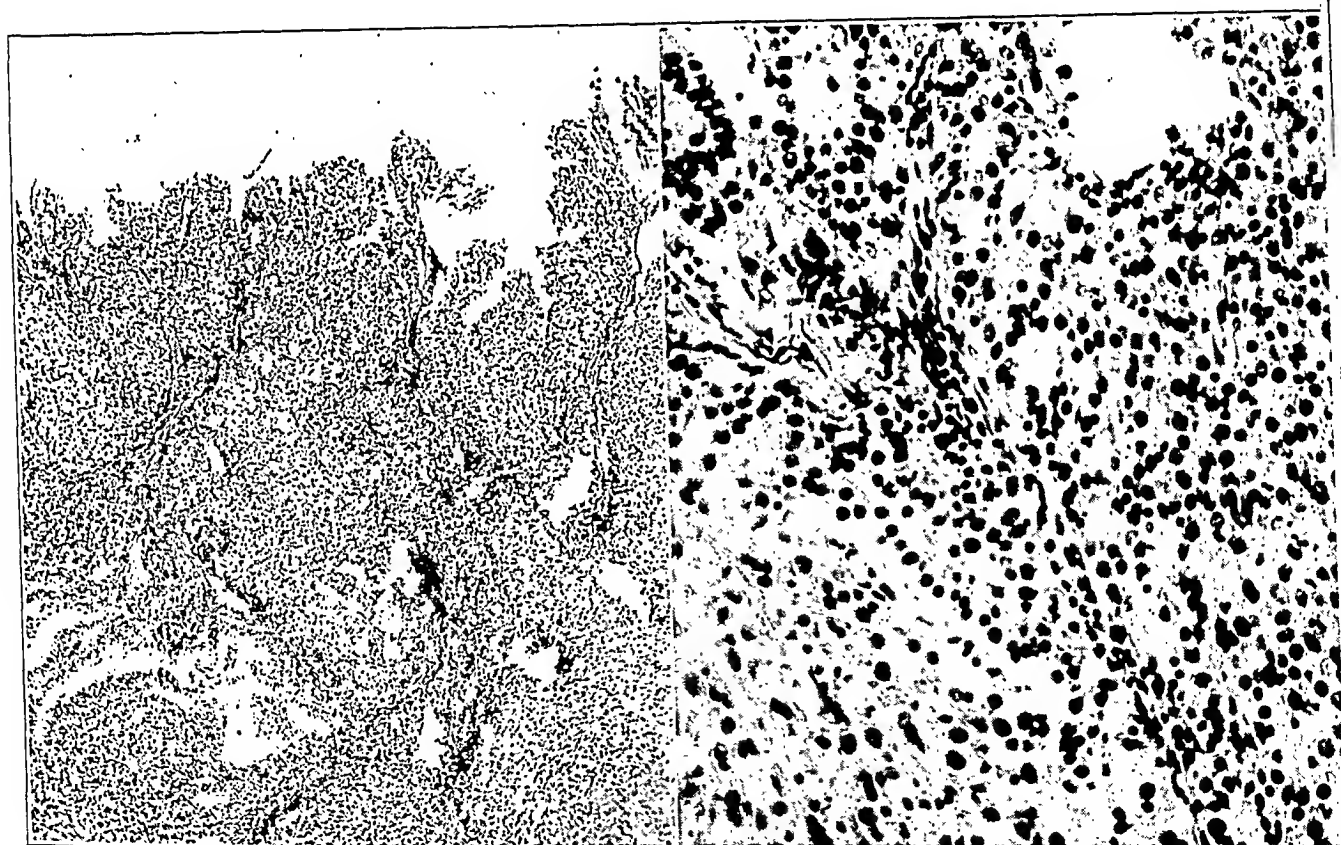


Fig. 10 (case 5).—Low and high power photomicrographs from the largest polyp, showing adenocarcinoma.

On June 26, when last seen, he had lost 16 pounds (7.3 Kg.) since his operation, was vomiting everything he tried to swallow and was rapidly losing ground. It was believed that he had an extensive carcinomatous involvement. He died at his home a few weeks later, and autopsy was not obtained.

The specimen removed at operation consisted of the lower half of the stomach, and presented a large flattened polyp (fig. 13) attached to the posterior wall by a fairly firm stalk. The tumor mass measured 8 cm. in diameter and, on microscopic study, proved to be a medullary carcinoma (fig. 14).

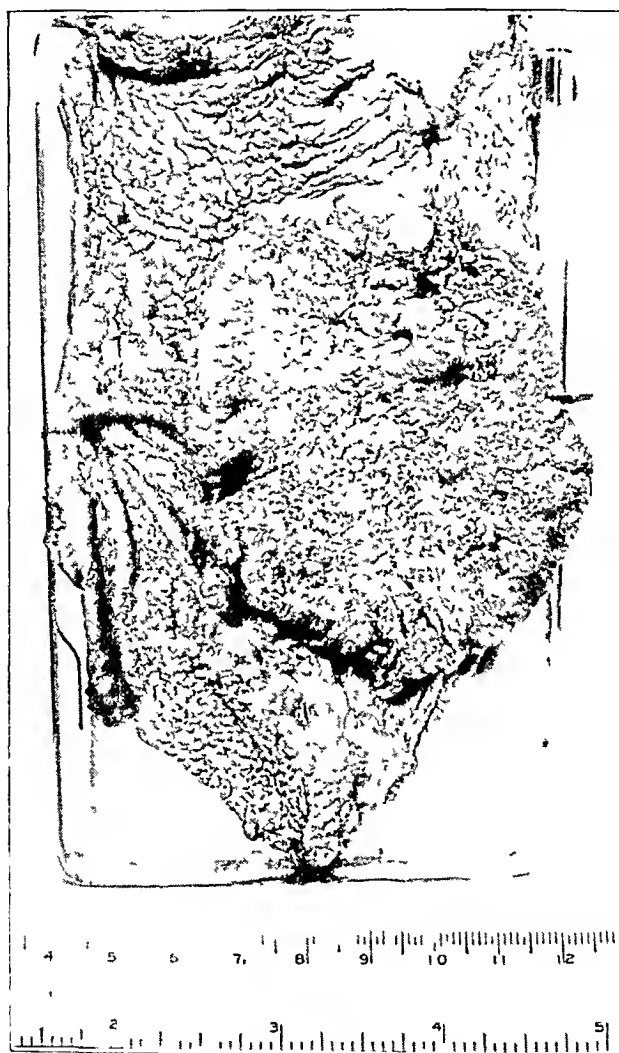


Fig 13 (case 6).—Photograph of the specimen removed at operation, showing a large flattened polyp

CASE 7.—W. C. H., an Englishman, resident in the United States for twenty-three years, aged 44, a master mechanic, became a private patient of one of us (T. G. M.) on July 2, 1928. Six months previously he had noted that his feces were black, and from that time had felt distinctly below par. He had had no definite gastric symptoms, except that when late for a meal he often felt unduly hungry. One day in early June, anorexia and fleeting abdominal pains developed. That evening he became nauseated and vomited several pints of chocolate-colored fluid with blood clots, subsequently having tarry stools. After ten days in bed,

curvature. It gave the impression of being a polyp. A subtotal gastrectomy with the Polya type of anastomosis was performed. One subsequent transfusion of 500 cc. of blood was administered, and the patient made a good recovery, being discharged on November 28, though still anemic (hemoglobin, 43 per cent).

His weakness persisted; he became aware of some difficulty in swallowing food, and epigastric pain developed, which he had not had previous to the operation.



Fig. 12 (case 6).—Roentgenogram, viewed from behind, showing the large filling defect along the greater curvature. Roentgenologic diagnosis: large carcinoma of the stomach or a benign polyp (1927).

On March 8, 1928, reexamination of the digestive tract by the roentgen rays showed an obstacle to swallowing at the lower end of the esophagus, and suggested some infiltration of the gastric wall and a new growth in the fundus of the stomach.

A review of the films made at the original examination then showed evidence of such a fundal lesion that had not been appreciated previously.

produced obstruction and seemed to project into the duodenal cap (fig. 15). The roentgenologist's diagnosis was a carcinoma or a large polyp of the pyloric end of the stomach.

Operation by one of us (E. L. E.) two days later revealed at once a gastric polyp that could be pushed back and forth through the pyloric ring. When the stomach was opened, two nodular and ulcerated masses were seen attached to the

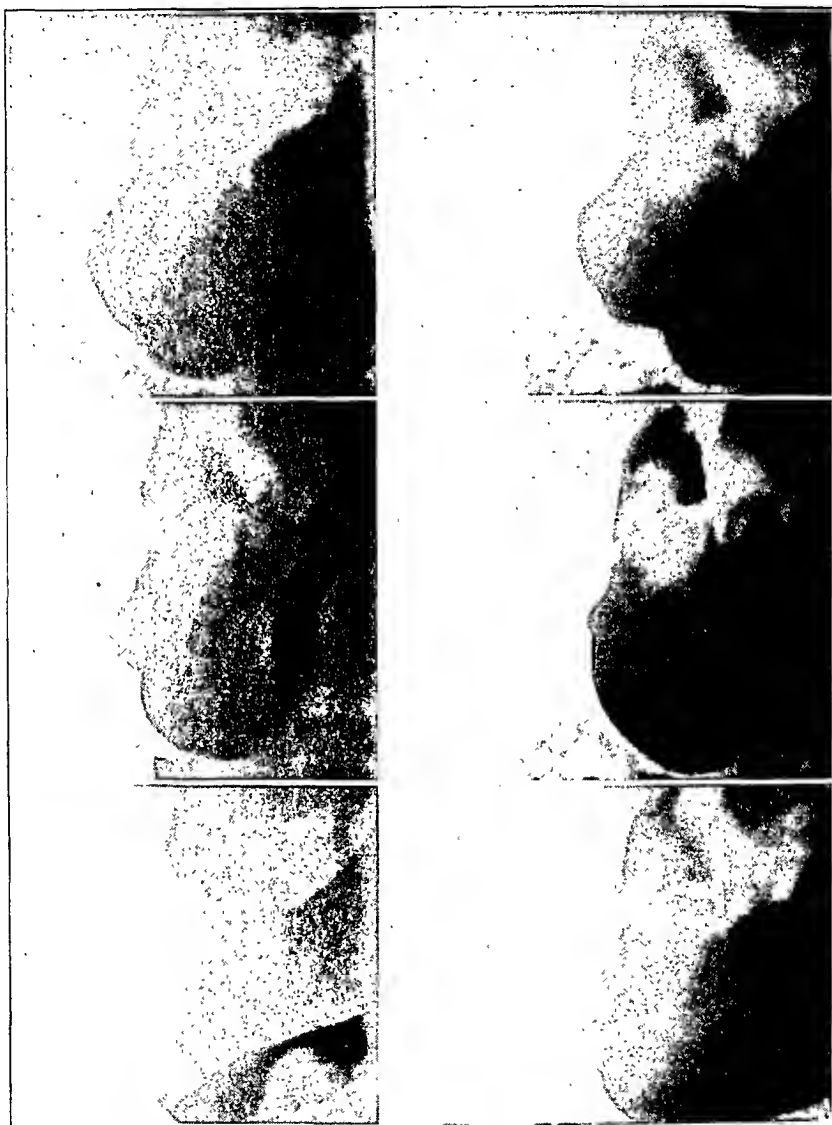


Fig. 15 (case 7).—Serial roentgenograms, viewed from in front, showing a marked filling defect of the pylorus with extension into the duodenal cap. Roentgenologic diagnosis: carcinoma or large polyp of the pyloric end of the stomach (1928).

posterior gastric wall near the pylorus. The smaller one of these could easily reach and enter the duodenum. On gross inspection, neither of the polyps suggested malignant degeneration, but a gastroscope revealed a single, whitish, indurated plaque higher in the stomach, which strongly suggested malignant change. A single

under the observation of a local physician, he returned to his work, but on June 30, he suffered from much dizziness and increasing weakness, with a return of blood in the stools, and was forced back to bed. He had lost 7 pounds (3.2 Kg.).

Physical examination showed only some tenderness just to the left and below the umbilicus. No masses were felt. No pallor or other signs of shock were observed. The red blood cells numbered 4,000,000, and the hemoglobin amounted to 80 per cent. The leukocytes numbered 5,000, and the differential count was normal. The feces showed no blood grossly, but the test for occult blood was

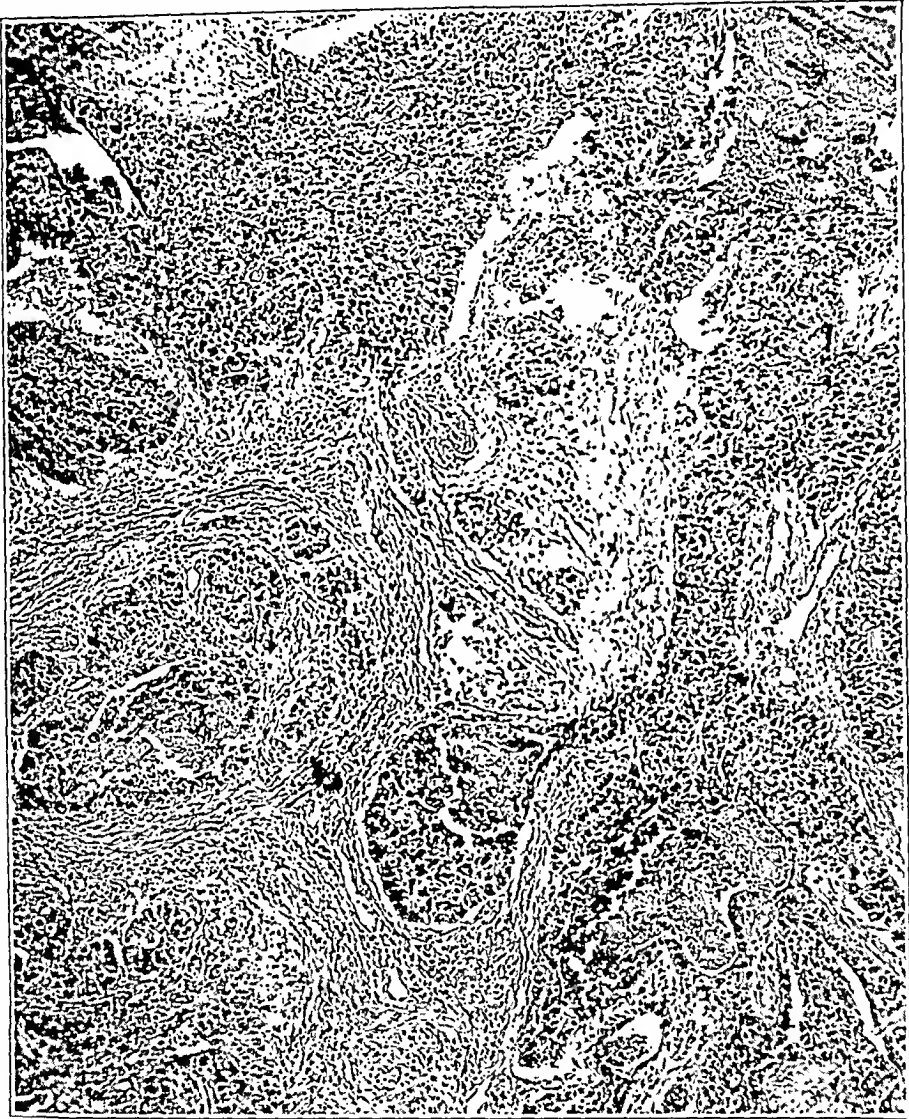


Fig. 14 (case 6).—Low power photomicrograph of polyp, showing medullary carcinomatous changes.

positive. A fractional gastric analysis, cautiously done on the following day, revealed a complete absence of free hydrochloric acid; this was later confirmed by a histamine test. The Wassermann reaction was negative. The blood pressure was 98 systolic and 75 diastolic. On July 16, after two weeks' rest and the Andresen diet for gastric hemorrhage, roentgenologic study of the gastro-intestinal tract showed a moderate gastric residue, hypoperistalsis and hypomotility of the stomach and a large pyloric defect which interfered with the peristaltic waves,

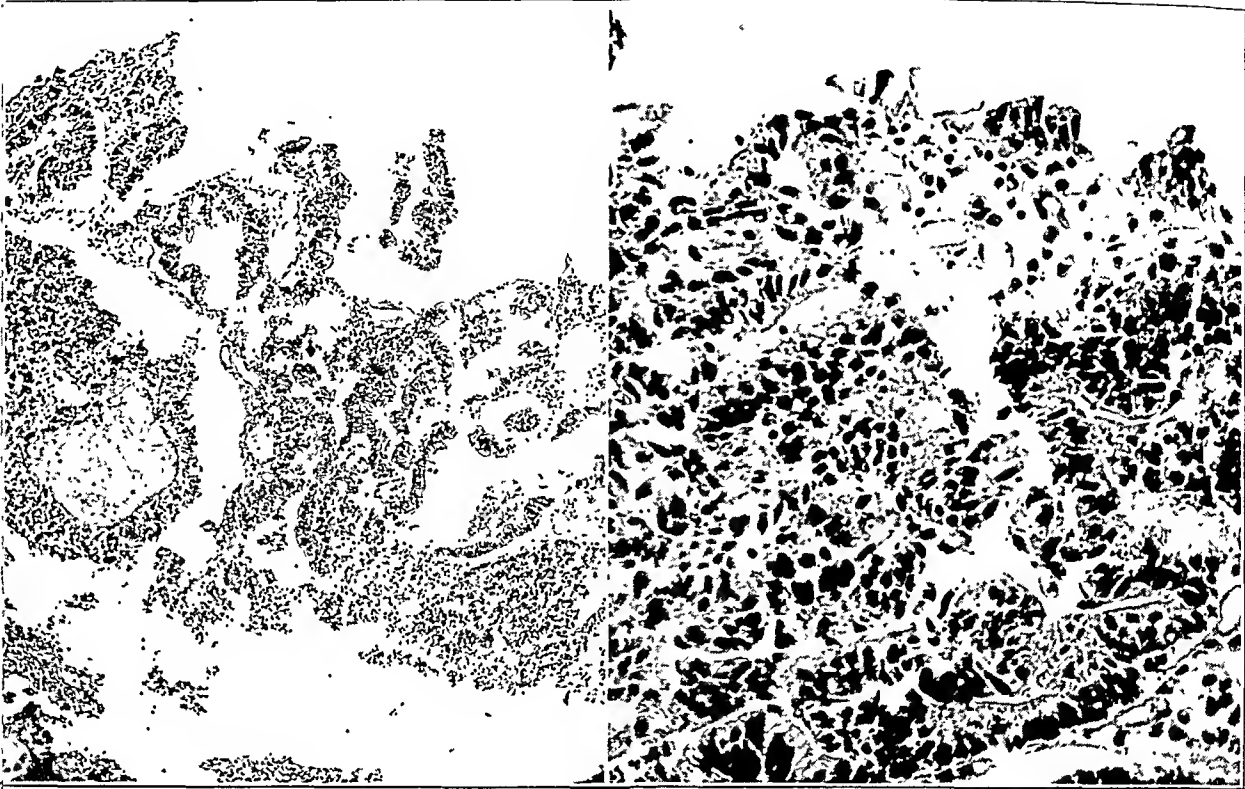


Fig. 17 (case 7).—Low and high power photomicrographs of larger polyp, showing malignant degeneration.

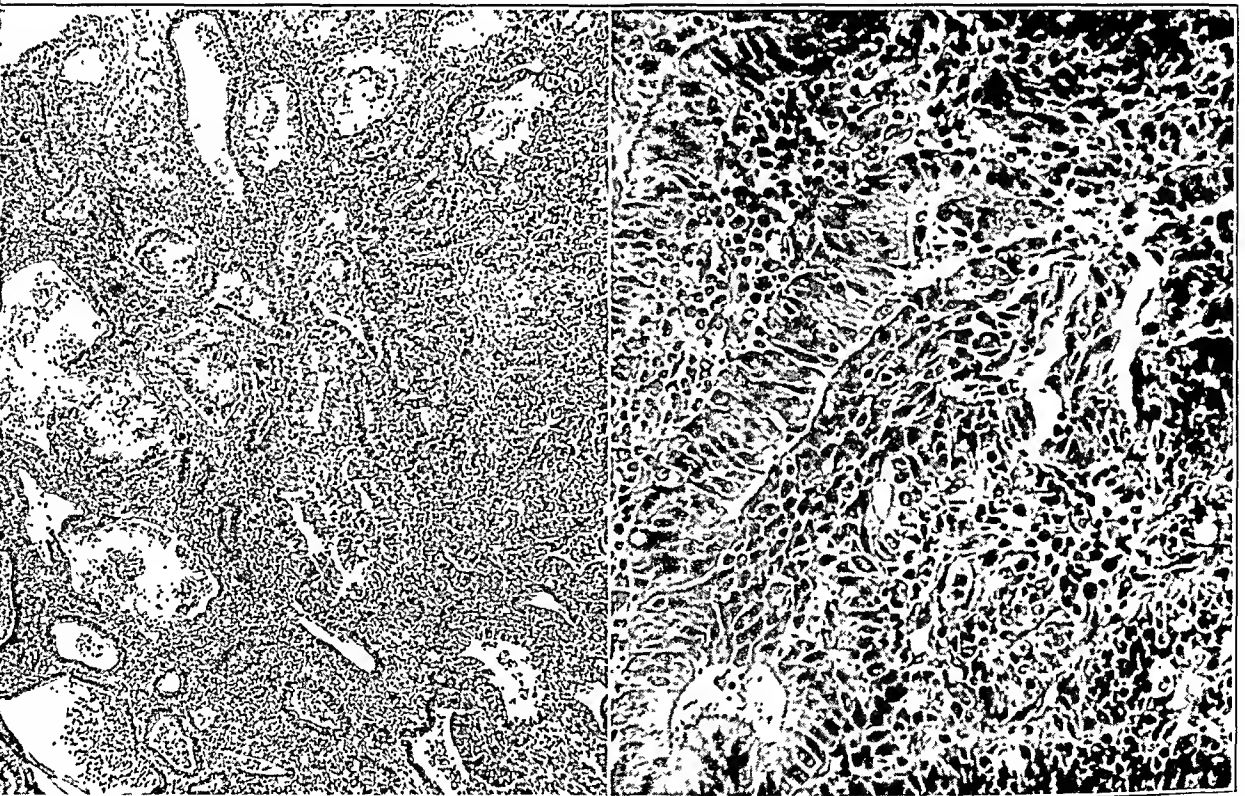


Fig. 18 (case 7).—Low and high power photomicrographs from smaller polyp, showing malignant degeneration.

hard node was felt in the omentum. Accordingly, a subtotal gastrectomy with Polya anastomosis was performed.

A good recovery was accomplished, and the patient left the hospital on August 15.

On Feb. 23, 1929, he reported that he had been back at work since early September, that his appetite was good and that with frequent small feedings he was gaining weight steadily. His weight was then half a pound (0.2 Kg.) greater than on July 2, 1928. He had no abdominal symptoms.



Fig. 16 (case 7).—Photograph of the specimen removed at operation, showing polyps. One of the polyps could easily be pushed beyond the line of the pyloric ring.

On Aug. 5, 1929, he weighed 137 pounds (62.1 Kg.), which was his normal weight. He had no symptoms, and had been working steadily. He was eating three regular meals daily, his appetite being good at all times. Physical examination of the abdomen gave negative results.

The specimen removed consisted of the lower third of the stomach with a small portion of the duodenum (fig. 16). The two polyps were attached to the posterior wall by pedicles, the largest polyp measuring 4 by 2.5 by 1.5 cm., and the smaller one, 2 cm. in each diameter. The plaque measured 1 cm. in each diameter.

At that time his blood showed: 3,100,000 red cells, 8,000 leukocytes and a hemoglobin percentage of 65. The platelets numbered 238,000. Four per cent of the red cells were reticulated. The urea nitrogen of the blood amounted to 14 mg. per hundred cubic centimeters. The van den Bergh test showed a delayed direct reaction and an indirect reading of 0.5 units. The Wassermann reaction was negative.

The patient improved with rest in bed and cardiac stimulation. Then, because of a tentative diagnosis of primary anemia and our routine practice in such cases, a fractional gastric analysis and a roentgenologic study of the digestive tract were undertaken.

The gastric analysis, with and without histamine, showed complete achlorhydria. On February 25, the roentgenologic study showed a marked gastric residue, a moderate continuous hyperperistalsis with motility less than commensurate and vacuolization in the middle third of the stomach (fig. 19). It was thought at first

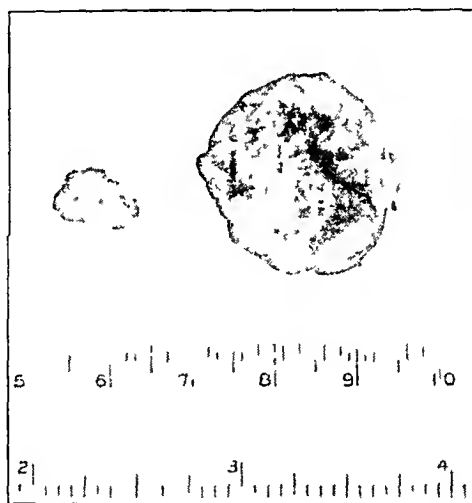


Fig 20 (case 8).—Photograph of two specimens removed at operation.

that the vacuolization was due to food particles, but a repetition of the examination three days later, after twenty-hour hours on only liquid food, showed the same defects. A diagnosis of polyposis with possible malignant degeneration was then made.

In spite of the patient's circulatory condition and anemia, and especially because of his continued and constant loss of blood by the bowel, surgical intervention was determined on

At operation under splanchnic anesthesia, one of us (E. L. E.) discovered a large polyp, which, when the stomach was opened, was seen to be about the size of a walnut and to be ulcerated. It was removed by severing its pedicle. Numerous smaller polyps were seen, but only one was removed.

The patient made a satisfactory surgical convalescence without complications and was discharged on April 2. On July 9, he reported to our followup clinic in excellent condition. He had regained his normal weight, had a good color and felt as well as ever. His heart was not enlarged. Blood counts were normal. No edema was present, and the abdomen showed only the incisional scar. A gastric specimen showed a persistence of the achlorhydria.

The polyps, especially the larger one, were ulcerated, and both proved under microscopic study to be papillomatous and undergoing malignant degeneration (figs. 17 and 18).

CASE 8.—J. Q., a groceryman, aged 52, was admitted to one of our medical wards on Feb. 4, 1929, because of extensive edema of the legs and external genitalia. He had begun to have evidences of cardiac decompensation six months previously: palpitations, dyspnea, cough, cyanosis and edema. He had also been very pale, and a study of his blood before admission had showed the red blood cells reduced to



Fig. 19 (case 8).—Roentgenogram, viewed from in front, showing areas of vacuolization in the middle and lower thirds of the stomach. Roentgenologic diagnosis: polyposis of the stomach with possible malignant degeneration (1929).

1,110,000, the hemoglobin to 36 per cent and the white blood cells to 4,800. A diagnosis of primary pernicious anemia had been made, and he had been on a liver diet.

Examination revealed, in addition to the pallor and peripheral edema, orthopnea, fluid in the pleural cavities, an enlarged heart with impaired sounds, an enlarged liver, a pulsus alternans and considerable sclerosis of the peripheral blood vessels. The vibratory sense was diminished in each leg, but no other evidence of involvement of the cord was found.

TABLE 1.—*Personal Group of Cases Showing Carcinomatous Change in Polyp of the Stomach*

Case	Year of Admission to Hospital	Sex; Age	Symptoms	Physical Observations	Observations on Gastric Analysis	Was main Reaction	Roentgenologic Observations				Diagnosis	Operative Operation Performed	Pathologic Observations	Comment
							Resi-	Peri-	Mo-	De-				
							duc	stalsis	tility	fect				
1 F. A. D.	1919	M 31	Hemorrhage 18 months before; anorexia and pain in left upper quadrant for 2 months	Mass; visible peristalsis; Ewald gland	Achylorhydria	—	4	+	—	+	Gastric papilloma, possibly malignant	Polyp on greater curvature; metastasis	Papilloma with malignant change	Diagnosed primary anemia 18 months before operation; died
2 E. K.	1923	M 45	Epigastric discomfort; later gnawing pain, relieved by food; hematemesis; lost 40 pounds; severe pain while under observation	Tenderness in epigastrium; enlarged liver	Achylorhydria	—	3	+	—	+	Duodenal ulcer or adhesions	Polyp on posterior gastric wall near pylorus	At autopsy; carcinoma at cardia; papilloma, with malignant changes at pylorus	Original clinical diagnosis was peptic ulcer (before admission); died
3 G. L.	1924	M 45	Gnawing epigastric pain for 7 years; pain increased by activity; lost 20 pounds in last year	Negro; no abdominal observations	Achylorhydria	—	0	±	+	+	Papilloma or nodular carcinoma of pyloric region	Three polyps on posterior wall	Papillomas with malignant change	Living after 5 years, and no evidence of recurrence
4 J. M.	1927	M 45	Nausea, vomiting, epigastric distress for 3 weeks; lost 15 pounds	Tenderness in gastric area	Achylorhydria; retention blood	—	4	0	—	+	Probable carcinoma of pylorus, but syphilitic lesion possible	Polyp in duodenal bulb; infiltration of lower third of stomach	Adenocarcinoma of polyp with intramural abscess; carcinoma of gastric wall	Died of secondary malignant lesions 18 months later
												Partial gastrectomy		

The specimen removed at operation (fig. 20) was ulcerated, and microscopic study showed it to be an adenocarcinoma (fig. 21).

The pertinent data on these eight cases of carcinomatous gastric polyp, which are outlined in table 1, may be summarized as follows:

1. All but one were males.
2. The majority (five of eight), at the time of recognition of the disease, was within the fifth decade of life, while one was 31 years of age, one was 52, and one was 61.

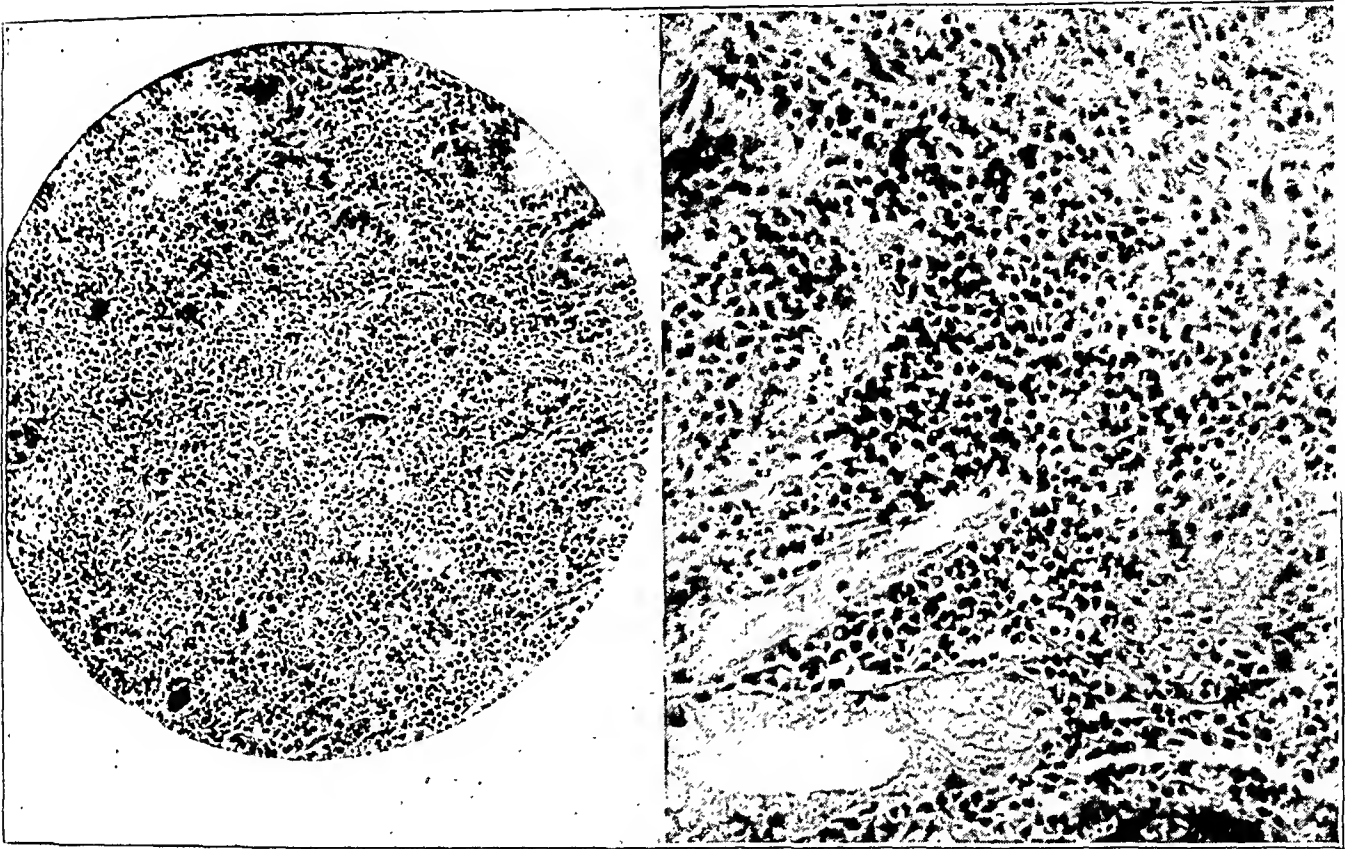


Fig. 21 (case 8).—Low and high power photomicrographs of larger polyp, showing adenocarcinomatous change.

3. The symptoms, in their order of frequency, were epigastric discomfort or pain, loss of weight, anorexia, vomiting that was sometimes bloody, nausea, pallor, the passage of blood by bowel, dizziness and diarrhea.

4. The physical signs were epigastric tenderness, the evidences of loss of weight and of anemia and Ewald glands (two cases).

5. Achlorhydria was present uniformly.

6. The Wassermann reaction was negative in every instance.

7. Roentgenologic study usually showed no interference with gastric peristalsis, a tendency to a decrease in gastric motility with retention of a part of the barium meal after six hours and invariably a vacuole defect in the stomach or duodenum.

8. A positive diagnosis of polyp with the suggestion that it might be malignant was made by the roentgenologists (Dr. H. K. Pancoast and Dr. E. P. Pendergrass) in two cases, and it was given as an alternate diagnosis with ordinary gastric carcinoma in three others; in two instances a probable carcinoma was suggested, and in one an ulcer or adhesions.

9. In all of the cases the polyp or polyps were demonstrated at operation.

10. One or more polyps in each case showed carcinomatous change, although polyps without such demonstrable degeneration were encountered.

11. At operation, excision of one or more polyps was done in four instances, a subtotal gastrectomy in three, and a sleeve resection in one.

12. Death occurred soon after operation in the first two cases, in both of which the disease was far advanced, and in two others it followed an extensive recurrence, in one twelve months, and in one eighteen months, after operation. Of the four patients living, one has a recurrence with hepatic metastasis, but the other three are well, a year, a year and a half and five years, respectively, after operation.

CASES FROM THE LITERATURE

Data of the same nature as those given in table 1 for our eight personal cases of malignant gastric polyps have been collected, as far as possible, on the twenty-four acceptable cases found in the literature. These data are assembled in table 2, and may be summarized as follows:

1. The male sex predominated, seventeen of twenty-one whose sex is known being men.

2. The age distribution was greater than in our personal series, ranging from 35 to 78 years. The great majority (81 per cent), as in our group, was 40 or more years of age.

3. The symptoms, in their order of frequency, were: abdominal pain, weakness, vomiting, anorexia, nausea, hematemesis, anemia and diarrhea.

4. The physical signs were chiefly those incident to anemia and epigastric soreness, although muscular rigidity, cachexia and a palpable mass were occasionally described.

[illegible]

111 - (CASES OF) Carcinomatous Gastric Polyp Collected from the Literature

Author; Date of Report	Sex; Age	Clinical Notes	Hydrochloric Acid in Gastric Contents	Pathologic Gastric Observations at Operation (o) or Autopsy (a)	Nature of Operation	Comment
Menetrier: <i>Bull. Soc. anat. de Paris</i> , 2: 736, 1886	M 35	No gastric symptoms.....	..	Many polyps, some malignant and ulcerated; metastases to liver (a)	Died of pneumonia; said to be first case of malignant gastric polyp reported
Menetrier: <i>Arch. de physiol. norm. et path.</i> , 1: 2: 236, 1888	F 70	Epigastric pain for 5 years, diarrhea, blood in stools, cachexia	..	Malignant adenomatous polyps with metastases (a)	Referred to as "polyadenome polypeux," but description suggests malignancy
Broë: <i>Arch. gén. de méd.</i> , 191: 135, 1903	M 60	Cardiorenal symptoms but no gastric symptoms	..	Pedunculated tumor, size of orange, near pylorus with carcinomatous change in center (a)		
Menetrier and Clunet: <i>Bull. et mém. Soc. de méd. d. hôp. de Paris</i> , 24: 419, 1907	M 75	No digestive symptoms, only those of kidney disease; cardiac enlargement, edema, dyspnea	..	Three small polyps and two larger sessile malignant tumors penetrating gastric wall (a) A sessile tumor in pylorus with malignant change, the latter extending into wall; benign polyp on posterior wall (a)		
Versey: <i>Arch. n. d. path. hist. zu Leipzig</i> , 1: 1, 1908	M 78	Pain, anorexia, nausea, vomiting of blood, weakness	..	Two soft malignant adenomatous polyps on greater curvature, one near pylorus (a) A malignant adenomatous polyp near pylorus (a)		
Winternitz and Boggs: <i>Bull. Johns Hopkins Hosp.</i> , 20: 1910	F 42	Negro; alcoholic; weakness and vomiting; arteriosclerotic and emaciated; ascites and many subcutaneous nodules	..	Many benign and malignant polyps (a)	Associated with elrhrrosis of the liver, subcutaneous hemangio-endotheliomas and intestinal lymphangio-endotheliomas; Wassermann reaction neg.

5. Gastric analyses were recorded in only nine instances, and in eight of these achlorhydria was present. One of the eight cases (Struther's), which was studied two years and also nine months before malignancy was discovered, showed some free hydrochloric acid on those two occasions, but later there was an entire absence of such acid in the gastric contents. The only case showing any free hydrochloric acid (Meyer and Bram's case) had an associated ulcer near the pylorus, and malignancy was found only in the central portion of one of the many polyps (obviously an early case).

6. Wassermann reactions were reported in six instances, being clearly negative in all, although one patient had previously had a chancre and a positive reaction.

7 and 8. Roentgenologic study was made in thirteen cases, but the detailed observations were not reported in most instances. In all of these, however, defects in the gastric shadow were noted, and in five the diagnosis of a polyp or polyps was made; in the others, the ordinary type of carcinoma or an ulcer was suspected. These were the diagnoses made in our personal cases when the correct lesion was not appreciated.

9. The diagnosis of a polyp was made at operation in fifteen cases; in the remainder the lesion was discovered at necropsy. In three cases (one of Heinz, one of Brunn and Pearl and one of Chosrojeff) tumor tissue was recovered from the stomach by lavage, thus affording a diagnosis of malignancy.

10. As far as could be determined, ten of the patients presented malignant adenomas, while three were referred to as having malignant papillomas; the others were merely said to have malignant polyps. Sixteen had multiple polyps, and one (that of Lamas), like one of ours, had an abscess in a polyp.

11. The operations performed included five partial gastrectomies, eight excisions of one or more polyps and two gastrojejunostomies.

12. Of the fifteen patients operated on, we know only that two died promptly of surgical shock, three died later (in from three to twelve months) of a malignant process, one died after seven months of nephritis and one was living after eighteen months.

COMMENT

Pathogenesis.—The benign intragastric polyps are, in our experience, usually of an adenomatous construction, most of them being of the compoundly papillomatous type, and some of the smoothly papillomatous type. Certain authors, as Brunn and Pearl,⁶ prefer to speak of them as adenopapillomatous. The early French writers, in referring to the cases of multiple polyp or of polyposis, preferred the term polyadenoma,

TABLE 2.—Cases of Carcinomatous Gastric Polyp Collected from the Literature—Continued

Author; Date of Report	Sex; Age	Clinical Notes	Free Hydrochloric Acid in Gastric Contents	Roentgenologic Observations	Pathologic Gastric Observations at Operation (O) or Autopsy (U)	Nature of Operation	Comment
Brunn and Pearl: Surg. Gynec. Obst., 43: 354, 1926	M 53	Pain, anorexia, nausea, weakness; epigastric tenderness; anemia (hemoglobin 55 per cent)	0	Filling defects on greater curvature, diagnosed polyps	Mass of polyps, size of orange, on greater curvature, with metastases to glands (O)	Excision	Died of shock from operation; achylia 25 years before; 9 months before this operation had resection for ulcer which was benign; emaciated 32 years; Wassermann reaction positive; then after treatment, negative
Brunn and Pearl: Ibid.	M 58	Weakness, dyspnea, edema, loss of weight; cachexia and anemia (hemoglobin 40 per cent)	0	Filling defects along greater curvature, one near cardia; diagnosed polyps	Malignant adenopapillomatous polyps on posterior wall near greater curvature, showing ulceration (O)	Cautery excisions of large polyps	Malignant tissue recovered from lavage led to diagnosis of probable malignant polyps; well for 17 months, then mass felt; Wassermann reaction negative
Brunn and Pearl: Ibid.	M 45	Pain for 18 months, anorexia, eructations, weakness, dizziness, vomiting, weight loss; alcoholic; cachexia and anemia (hemoglobin 52 per cent)	0	Filling defects, diagnosed multiple polyposis	Fourteen adenopapillomatous polyps with malignant change; wall of stomach and glands involved one polyp ulcerated (O)	Partial gastrectomy	Died of shock from operation
Balfour and Henderson: Ann. Surg. 85: 354, 1927	..	Anemia.....	0	Malignant polyp in upper third of stomach (O)	Cautery excision	Inoperable carcinoma of stomach 4 months later
Lamas: Arch. d. mal. de l'app. digestif 18: 261, 1928	M 50	Pain, vomiting of blood; epigastric tenderness	..	Niche on lesser curvature, diagnosed ulcer	Diffuse polyposis with malignant change in one of large polyps; abscess in polyp (O)	Excision	Immediate result satisfactory
Horsley: Ann. Surg. 88: 554, 1928	M 77	Indigestion for 2 years; nausea, vomiting and weight loss; emaciation	..	Pyloric obstruction	Malignant polyp at pylorus; malignant ulcer associated (O)	Partial gastrectomy	Died 7 months later from nephritis

Chosrojeff: Beitr. z. path. Anat. u. z. allg. Path. 54: 596, 1912	M 36	Bloody diarrhea for 2 years; epigastric pain, anorexia and weight loss; anemia; mass palpated	Malignant polyps of adenomatous type with metastases (o)	Cautery excision of some polyps	Blood and tumor tissue in lavage water, which led to diagnosis of polypoid adenoma; good recovery from operation
Heinz: Cor-Bl. f. Schweiz. Aerzte 42: 354, 1912	M 35	Pedunculated tumor	Three malignant adenomatous polyps (o)	Excision of 3 polyps	Tumor tissue in lavage water; developed severe anemia after operation
Chiarre: Deutsche med. Wehnschr. 39: 2349, 1913	F 44	Malignant adenomatous polyps at pylorus (a)	Pylorus intussuscepted into duodenum
Finney and Friedenwald: Am. J. M. Sc. 154: 693, 1917	Papillomatous polyps throughout stomach with malignant change in some near pylorus	Museum specimen, College of Physicians, Baltimore
M 50	Pain, nausea, vomiting, weakness, loss of weight for 9 months; poorly nourished, large liver, epigastric mass; melena	0	Carcinoma of stomach	Malignant papillomatous polyp near pylorus and serirrhous carcinoma of stomach wall; metastasis to glands (o)	Resection and posterior gastrojejunostomy	Immediate result satisfactory	
M 55	Weakness and loss of weight for 3 months; anemia and melena	0	Carcinoma of stomach	Single adenopapilloma with broad base (sessile) with ulceration and malignant change (o)	Cautery excision	Died of carcinoma of stomach a year later; Wassermann reaction negative	
Gassman: Arch. f. Verdauungskr. 28: 226, 1921	M 57	Indigestion for years; pain, anorexia, loss of weight for 2 months	0	Polypoid tumor	Malignant adenomatous polyp, size of apple, on lesser curvature (o)	Excision	Immediate result satisfactory; gained 5 pounds in 5 months
Zabel, quoted by Bryan: Southwest Med. 6: 223, 1922	Malignant papilloma (a)	Megastoma intestinale in tumor mass
Struthers: Surg. Gynec. Obst. 38: 610, 1924	M 48	Pain in epigastrium and back for a year; weakness, constipation, anemia	20	Lesion at pylorus	Hypertrophied pyloric mucosa producing obstruction (o)	Gastrojejunostomy	First admission to hospital; Wassermann reaction negative
		Pain increased; vomiting....	20	Gastrojejunal ulcer	Gastric polyposis obstructing both outlets from stomach (o)	Partial gastrectomy	Second admission 15 months later
		Pain, nausea, vomiting, weakness, anemia	0	Carcinoma of stomach	Carcinoma with metastases to ribs	Third admission 9 months later; died 3 months later
Meyer and Brams: Surg. Gynec. Obst. 41: 311, 1925	M 53	Periodic attacks of pain relieved by vomiting for 2 years; anorexia, nausea, weight loss, tenderness in left upper quadrant	15	Defect on lesser curvature near pylorus; probably carcinoma	Typical peptic ulcer near pylorus and many polyps nearby; polyps not ulcerated but one showed malignancy in center (o)	Resection	Earliness of case and ulcer probably explain acidity; (only case showing any free hydrochloric acid); Wassermann reaction negative

Also, the frequent occurrence of benign polyps in the stomach, the seat of ulcer or carcinoma, suggests an inflammatory origin for the polyps. Chronic gastritis is commonly associated with these two diseases of the stomach. Douglas,²⁰ Mills² and Stewart²¹ each reported a case of gastric carcinoma with associated benign polyps. Both Douglas and Stewart believed that the carcinoma might have originated in a similar benign polyp, but Mills expressed the opinion that this had not occurred in his case because of the distance of the malignant lesion from the benign ones and its fundamentally different structure. However this may have been, one may assume that a chronic gastritis was present. In Meyer and Brams'²² case of gastric polyps, one of which was carcinomatous, there was an ulcer near the polyps, and other such cases have been reported. Here again one can easily conceive of a localized inflammation about the ulcer as a basis for the polyp formation.

Other etiologic factors, such as hereditary influences, congenital malformations, systemic lymphatic hypertrophy, metabolic disturbances, alcoholism, sclerosis of gastric vessels and such specific chronic infections as syphilis and tuberculosis, have been suggested; there is not sufficient evidence, however, to justify further consideration of these possible factors at this time.

The development of malignancy in benign gastric polyp is favored by trauma incident to gastric peristalsis and to the passage of coarse articles of food and also by the adenomatous nature of the benign lesion. Ewing¹⁵ suggested that all the bulky polypoid carcinomas of the stomach may have their origin in such benign polyps.

The possibility of a carcinomatous polyp springing directly from a primary malignant process in the gastric wall cannot, of course, be denied. Our case 6, presenting a polypoid medullary carcinoma with a thick firm stalk, may be an instance of such development. In all the other cases, however, no gross evidence of malignant involvement of the pedicle or of the wall of the stomach itself was present, and gastric peristalsis, as indicated by fluoroscopic study, was not interfered with. That the lesions in most instances had assumed the form of polyps before malignancy developed is suggested also by their frequent association with other polyps still benign, by the observation, in some of them, of malignant change in only a small area of an affected polyp and by the long duration of some of the polyps before the evidences of serious illness were manifest.

20. Douglas, J.: Benign Tumors of the Stomach, *Ann. Surg.* **77**:580 (May) 1923.

21. Stewart, M. J.: Carcinoma of the Stomach in Association with Multiple Polypoid Adenomata, *J. Path. & Bact.* **18**:127, 1913.

22. Meyer, K. A., and Brams, W. A.: Non-Carcinomatous Tumors of the Stomach, *Surg. Gynec. Obst.* **41**:311 (Sept.) 1925.

and Menetrier¹⁴ divided them into the diffuse form (polyadénome polypeux) and the localized form (polyadénome en nappe). Although adenoma is the term most commonly used, a capsule is not usually found. This led Mills⁵ to look on them as papillomas rather than adenomas. He expressed the belief that they begin as simple thickenings of the mucous membrane, later becoming sessile growths and finally true polyps. It is probable that they begin in much the same way that nasal polyps do, being at first merely low elevations of the mucosa and later becoming pedunculated. Ewing¹⁵ regarded these nasal polyps as pseudoneoplasms of inflammatory origin, although they may eventually assume various pathologic forms: fibromas, adenofibromas or myxomas. It would seem that the young gastric polyps might be regarded similarly as pseudoneoplasms, eventually taking on an adenomatous form and sometimes showing malignant degeneration.

This comparison with nasal polyps suggests that the gastric polyps have an inflammatory origin. Menetrier,¹⁶ who in 1886 reported the first case with malignant change, believed in such an origin, and called particular attention to their occurrence in patients with arteriosclerosis. Bret¹⁷ also noted this association in reporting a case with circulatory, but not gastric, symptoms. Although their reasoning is not convincing today, other arguments for an underlying inflammatory lesion may be presented. Chief among these is the fact that achlorhydria is so frequently associated, not only in the malignant cases, but also in those that are still benign. Strauss, Meyer and Bloom¹⁸ stated that in cases of polyposis, achylia is a constant observation. One of Brunn and Pearl's⁶ patients had achlorhydria twenty-five years before malignancy was discovered. Faber¹⁹ pointed out that achlorhydria results from chronic gastritis even when ordinary microscopic study shows no evidence of such a lesion. Furthermore, it is well known that polyps on other mucous membranes develop as a result of inflammatory changes: nasal polyps in cases of chronic rhinitis and colonic polyps in cases of chronic colitis.

14. Menetrier, P.: Des polyadénomes gastriques et de leurs rapports avec le cancer de l'estomac, *Arch. de physiol. norm. et path.* **1-2**:236, 1888.

15. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1922.

16. Menetrier, P.: Polyadénomes gastriques et cancer de l'estomac, *Bull. Soc. anat. de Paris* **2**:735, 1886.

17. Bret, J.: Du polyadénome polypeux et de l'adénopapillome de l'estomac, *Arch. gén. de méd.* **191**:1345, 1903.

18. Strauss, A. A.; Meyer, J., and Bloom, A.: Gastric Polyposis, *Am. J. M. Sc.* **176**:681 (Nov.) 1928.

19. Faber, K.: The Etiology and Pathogenesis of Achylia Gastrica, *Am. J. M. Sc.* **172**:1 (July) 1926.

malignancy cannot be determined macroscopically, nor often by the microscope except after numerous sections are made, is reason enough for radical treatment for every gastric polyp.

CONCLUSIONS

On the basis of the data set forth in this paper regarding eight personal cases of carcinomatous polyp of the stomach and regarding twenty-four cases previously reported in the literature, a total of thirty-two cases, we feel justified in presenting the following conclusions:

1. Carcinomatous polyp of the stomach is more frequent than has been generally believed, having been found in 35 per cent of all the cases of intragastric polyp that we have studied adequately (eight of twenty-three), and both the history and the pathologic data suggest that it usually originates in polyp of a benign nature.

2. The benign intragastric polyps that show this tendency to malignant change are usually of an adenomatous construction.

3. Most of the patients showing such malignant change are males (83 per cent), and the age incidence is the same as for mural gastric cancer.

4. The symptoms are those of any malignant gastric lesion with, in addition, those of the two other common consequences of gastric polyp—intermittent pyloric obstruction and hemorrhage.

5. The hemorrhage may be frank or occult; it not infrequently leads to an erroneous diagnosis of primary anemia (three of our eight personal cases). Consequently, gastric polyp should be considered in all cases of unexplained anemia.

6. Roentgenologic study alone often makes the diagnosis of gastric polyp, and malignancy may be suspected on the basis of the clinical picture.

7. Gastric polyp may be overlooked at operation, and special procedures, including gastrotomy and exploration of the interior of the stomach with a gastroscope, are indicated when any clinical suspicion of a polyp exists or when a suspected ulcer is not found.

8. All gastric polyps, when demonstrated, deserve the radical surgical treatment commonly employed in cases of known or suspected gastric carcinoma.

motility. Peristaltic waves are not usually interfered with because of the superficial attachment of the polyp to the wall of the stomach. Their frequency and depth are usually increased (hyperperistalsis). The defect appears as a vacuole, smooth in outline and usually situated in the pylorus or duodenum. Several such defects may appear. The presence of one such defect in the duodenal bulb may be associated with others in the stomach. It is conceivable that a duodenal vacuole may be found at one examination and not at another, although we have not had this experience. The motility also, doubtless, varies from time to time depending on the position of the polyp.

When a polyp is so demonstrated by roentgenologic study, and the symptomatology and observations of gastric analysis suggest malignancy, a diagnosis of carcinomatous polyp is justified.

Surgical Features.—When the polyp is small, or the pedicle long, extreme difficulty may be encountered in its discovery even by direct palpation of the viscera at operation. In the first patient operated on by one of us (E. L. E.) the accidental finding of an indefinite soft mass in the pyloric region which suddenly, during digital examination, slipped away and then later was found in the duodenum, from which, on palpation, it again promptly slipped back into the stomach, suggested the lesion. Because of this experience, when extragastric manipulation failed to reveal the mass in another case, in which polyp had been diagnosed by roentgen study, a gastrotomy was performed. When the stomach was opened, the lesion was readily made to protrude through the wound (case 3, illustrated in the original report).

Gastrotomy may thus establish the diagnosis in cases that would otherwise be overlooked even at operation. The fact that such polyps at their point of origin are usually attached only to the inner coats of the gastric wall accounts for the occasional difficulty of finding them without direct inspection of the interior of the stomach. A direct gastroscope is an aid in such investigation. Failure to open the stomach doubtless accounts for some of the negative operative observations in cases of suspected ulcer which are really cases of gastric polyp. Such patients would continue to have symptoms even if the usual gastrojejunostomy, as the surgical treatment for ulcer, was performed. Certainly when the clinical data suggest a polyp the stomach should be opened and explored.

The surgical procedures in cases of polyp must be suited to the condition found at operation. In view of the high incidence of malignancy in cases of polyp, the more extensive subtotal gastrectomy with removal of the lymph nodes is the wisest procedure. The former methods of local excision, cautery removal, ligation and removal and sleeve resection should give way to the more radical methods. The fact that

at the Mayo Clinic, found a basal metabolism below minus 15 per cent in 103 patients who had no disease of the thyroid.

A few persons who seemed to be healthy in spite of basal metabolisms of minus 19 to minus 25 per cent have been reported by Sturgis,⁷ Wishart,⁸ Strouse and Binswanger⁹ and King¹⁰ among men in the temperate zone, and by Sison and Ignacio¹¹ among Filipinos. In ten men (physicians, lawyers, engineers) between 23 and 40 years of age who had no apparent disease and who had lived all their lives in or near Rio de Janiero, De Almeida¹² found an average heat production 24 per cent lower than the average value of the Aub-Du Bois standard normal of 39.7 calories per square meter of body surface per hour. From these data he concluded that the metabolism of white men is lower in the tropics than in temperate climates.

It has been shown by Ohler and Ullian¹³ (37 cases), Higgins¹⁴ (43 cases), Lawrence¹⁵ (42 cases), and more recently by Koehler¹⁶ (288 cases), that a basal metabolism from 10 to 25 per cent below the standard normal, without myxedema, is not an infrequent observation. Most of these authors do, however, credit some degree of thyroid insufficiency for these low rates, and classify their cases as hypothyroidism, incipient hypothyroidism and thyroid failure without myxedema. Some of their patients apparently showed clinical improvement coincident with a rise

7. Sturgis, C. C.: A Clinical Study of Myxedema With Observations of the Basal Metabolism, *M. Clin. North America* **5**:1251, 1922.

8. Wishart, G. M.: The Variability of Basal Metabolism, *Quart. J. Med.* **20**: 193, 1927.

9. Strouse, S., and Binswanger, H. F.: The Symptom Complex Resembling Hyperthyroidism Without Increased Metabolism, *J. A. M. A.* **88**:161 (Jan. 15) 1927.

10. King, J. T., Jr.: Observations on the Menopause: I. The Basal Metabolism After the Artificial Menopause, *Bull. Johns Hopkins Hosp.* **39**:281, 1926.

11. Sison, A. B. M., and Ignacio, M.: Basal Metabolism Among Filipinos, *J. Philippine Islands M. A.* **7**:416, 1927.

12. De Almeida, A. O.: Le métabolisme minimum et le métabolisme basal de l'homme tropical de race blanche, *J. de physiol. et de path. Gén.* **18**:713, 1919.

13. Ohler, W. R., and Ullian, L. J.: Clinical Survey of 1000 Cases on Whom Basal Metabolism Studies Have Been Made, *M. Clin. North America* **8**:1495, 1925.

14. Higgins, W. H.: Management of the Hypothyroid, *South. M. J.* **20**:779, 1927; Incipient Hypothyroidism: A Clinical Study, *J. A. M. A.* **85**:1015 (Sept. 26) 1925.

15. Lawrence, C. H.: The Physiological Background for the Symptoms of Thyroid Failure, with a Consideration of the Results of Treatment, *Boston M. & S. J.* **196**:43, 1927; Thyroid Failure Without Myxedema, *M. Clin. North America* **8**:1779, 1925.

16. Koehler, A. E.: Differential Diagnosis Between Hypothyroidism and Hyposuprarenalism, *J. A. M. A.* **91**:1457 (Nov. 10) 1928.

LOW BASAL METABOLISM WITHOUT MYXEDEMA *

FRANCIS M. THURMON, M.D.

BOSTON

AND

WILLARD OWEN THOMPSON, M.D.

CHICAGO

In a study of low basal metabolism following thyrotoxicosis, Thompson and Thompson¹ were impressed by its frequency and by the fact that an underfunction of the thyroid could be demonstrated in only a comparatively small number of cases. Several of the patients appeared to be healthy in spite of low metabolism. These results made it appear desirable to make a study of low basal metabolism in general.

A low metabolic rate following toxic goiter has been observed by Elliott,² Jordan³ and Cabot⁴ in a few patients who did not appear myxedematous. Means and Burgess,⁵ in reviewing the basal metabolisms of the first 1,000 subjects on whom such a determination was made at the Massachusetts General Hospital, reported rates of minus 15 per cent or lower in 16 cases exclusive of disorders of the thyroid. Boothby and Sandiford,⁶ in summarizing the metabolism data of 8,614 subjects

* Submitted for publication, April 23, 1930.

* Aided in part by a grant from the Proctor Fund of the Harvard Medical School, for the Study of Chronic Diseases. All of the data for this paper were collected in the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital. Rush Medical College defrayed part of the expense of getting the data ready for publication after one of us (W. O. T.) had joined its faculty.

1. Thompson, W. O., and Thompson, P. K.: Low Basal Metabolism Following Thyrotoxicosis: I. Temporary Type Without Myxedema, with Special Reference to the Rôle of Iodine Therapy, *J. Clin. Investigation* **5**:441, 1928; Low Basal Metabolism Following Thyrotoxicosis: II. Permanent Type Without Myxedema, *ibid.* **5**: 471, 1928; Temporary and Permanent Myxedema Following Treated and Untreated Thyrotoxicosis, *ibid.* **6**:347, 1928; Significance of Low Basal Metabolism Following Thyrotoxicosis, *Am. J. Surg.* **7**:48, 1929.

2. Elliott, C. A.: Results of Thyroidectomy for Hyperthyroidism as Indicated by Examination a Year or More Following Operation, *Tr. A. Am. Phys.* **41**:93, 1926.

3. Jordan, S. M.: Basal Metabolic Rates and Their Relation to End-Results in Thyroid Disease: A Statistical Study, *Arch. Surg.* **11**:1 (July) 1925.

4. Cabot, R. C.: Case 12182, *Boston M. & S. J.* **194**:844, 1926.

5. Means, J. H., and Burgess, H. W.: The Basal Metabolism in Nontoxic Goiter and in Borderline Thyroid Cases, *Arch. Int. Med.* **30**:507 (Oct.) 1922.

6. Boothby, W. M., and Sandiford, I.: Summary of the Basal Metabolism Data on 8,614 Subjects With Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *J. Biol. Chem.* **54**:783, 1922.

enough desiccated thyroid¹⁹ to raise the metabolic rate to the normal level. It was thus inferred that in the majority there was no definite evidence of subnormal thyroid function.

In table 1, these 196 cases and 80 cases of myxedema²⁰ for which data were sufficient, are divided for comparison into groups on the basis of the metabolism tests alone. The low metabolism in each case has been averaged before being placed in its division. It is of interest that the basal metabolic rate was below minus 20 per cent in 84 per cent of the patients with myxedema, but in only 29 per cent of the patients without myxedema. Whereas in only 8 (4 per cent) of 196 patients without myxedema there was a basal metabolism below minus 25 per cent, in the 80 patients with myxedema there were 49 (61 per cent) with a basal metabolism below 25 per cent.

CLASSIFICATION

These 196 patients may be tentatively grouped as follows:²¹

- I. Those who appeared to be normal (11 patients).
- II. Those who appeared to be abnormal (185 patients).
 - A. Those who were nervous, worried, easily fatigued, and sensitive to cold, who often had diminished catamenia, and probably suffered from some endocrine disturbance (79 patients).
 - B. Those in whom the outstanding abnormality appeared to be irregularity of menstruation (always scantiness or temporary amenorrhea or both) (21 patients).
 - C. Those who probably had mild hypothyroidism, but who had no detectable edema (13 patients).
 - D. Those with various conditions not included in the preceding groups that are sometimes associated with low basal metabolism, e. g., starvation, pituitary tumor, muscular atrophy, etc. (72 patients).

I. *Normal Persons*.—There were 11 patients who, so far as we were clinically able to determine, were normal except for a basal metabolism lower than the accepted standard (minus 11 to minus 24 per cent). The following case history is presented as typical:

Mrs. M. H. (lab. no. 5745), a laboratory technician, aged 25, complained merely of sensitiveness to cold weather. There were no abnormal clinical observations, except a basal metabolic rate of minus 24 per cent. Two grains (0.13 Gm.)

19. Armour's desiccated thyroid was used in all cases.

20. These 80 cases of myxedema form an unselected group in which more than one basal metabolism determination was made before thyroid was administered. The data on the other cases of myxedema are less complete.

21. The classification given here is based largely on the symptoms presented by the patients and, for the most part, makes no attempt to differentiate clinical entities.

in metabolism during the administration of desiccated thyroid. Koehler was unable to classify many of his patients and considered some to have an underfunction of the suprarenal cortex, although the evidence on which this diagnosis is based is inconclusive.

The foregoing reports indicate that low basal metabolism without myxedema is a common observation, and that the types of patients falling within this classification are thought to be: (1) those who are apparently healthy and normally have a low metabolism; (2) those with hypothyroidism too mild to result in myxedema, and (3) those in whom a low metabolism is associated with pathologic conditions other than underfunction of the thyroid.

TABLE 1.—*Comparison of the Basal Metabolism in One Hundred and Ninety-Six Cases with Low Rates without Myxedema and in Eighty Cases of Typical Myxedema*†*

Basal Metabolic Rate, Per Cent Normal	Without Myxedema		With Typical Myxedema	
	Number of Cases	Per Cent of Cases	Number of Cases	Per Cent of Cases
Minus 11 to -15.....	27	14	3	4
-16 to -20.....	111	57	10	12
-21 to -25.....	50	25	18	23
Below -25.....	8	4	49	61
Total.....	196	100	80	100

* Aub-Du Bois standards were used in the calculations.

† The thirteen patients who apparently had hypothyroidism without myxedema are included among those without myxedema.

DATA

Of 6,655 patients of all types, 1,255 (19 per cent) had one or more metabolic rates below minus 10 per cent. Eliminating those cases in which the thyroid function seemed definitely subnormal (130 cases of myxedema and 16 cretins), those in which the diagnosis of myxedema was doubtful (26 cases), those in which data had been previously reported¹⁷ (50 cases), and those in which data were unsatisfactory,¹⁸ there remains a group of 196 cases which forms the basis of this paper.

These patients did not appear to be myxedematous, and most of them appeared to receive no clinical benefit from the administration of

17. Thompson, W. O., and Thompson P. K. (footnote 1, first, second and fourth references).

18. In this group are included 236 private patients of physicians outside the clinic, who were omitted because of varying criteria of diagnosis and our inability to secure complete data; and 538 patients who had either only one low basal metabolic rate among several normal ones, or a single determination which was low.

tation, excitability, irritability, headaches, indefinite gastro-intestinal irregularities, loss of weight and occasionally increased blood pressure were the most prominent symptoms in the group of patients described by Strouse and Binswanger⁹ as having a symptom-complex resembling hyperthyroidism without increased metabolism. Many of these symptoms were also present in the patients with "autonomic imbalance" but normal metabolism described by Kessel and Hyman,²³ and are also complained of by patients with "effort syndrome."

Thus it is at present impossible to be sure that the various clinical abnormalities and the reduction in basal metabolism in patients in group A are the results of the same pathologic condition. Many of the patients were referred to us with a diagnosis of neurasthenia. However, just because we do not at present know the diagnostic significance of the signs and symptoms these patients presented, is not a good reason for labeling them as neurasthenic types. It has previously been emphasized that these patients do not show a favorable clinical response to therapeutic doses of desiccated thyroid. Their metabolism may be raised to standard normal, but there is either no change in their condition or they may develop thyroid intoxication, i. e., palpitation, rapid pulse, increased nervousness and possibly precordial pain. The response to thyroid is, in our opinion, the single most important criterion in determining the presence or absence of underfunction of the thyroid.

The following case history is typical of the group:

Mrs. A. T. (figs. 1 and 2), an American housewife, aged 43, first came to the metabolism laboratory on March 27, 1928, complaining of headaches, ease of fatigue, sensitiveness to cold weather, coldness and numbness of the extremities, nervousness, insomnia and worry, all of which had been present as long as the patient could remember. At times the headaches were accompanied by nausea and vomiting. She had never been pregnant. The results of the physical examination were essentially negative. She was well developed and well nourished. The skin was soft, warm and moist, the hair of normal texture and distribution. The thyroid gland was barely palpable and of normal consistency. Examination of the chest, heart, abdomen, pelvis and rectum showed no abnormalities. There were no signs of myxedema. The systolic blood pressure was 140 mm. of mercury and diastolic pressure 80 mm. During the course of her visits to the clinic, laboratory studies revealed no abnormalities in the urine, a hemoglobin concentration of 80 per cent, a red blood cell count of 5,000,000 per cubic millimeter and a white blood cell count of 7,250 per cubic millimeter. Gastric analysis, roentgenograms of the sella turcica and of the gastro-intestinal tract, and food tests in the anaphylaxis clinic gave normal results. Special examinations of the eyes and ears showed nothing remarkable. The initial basal metabolic rate was minus

23. Kessel, L., and Hyman, H. T.: Studies of Graves' Syndrome and the Involuntary Nervous System: II. The Clinical Manifestations of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), *Am. J. M. Sc.* **165**: 513, 1923.

of desiccated thyroid daily caused the rate to rise to plus 5 per cent, but also caused palpitation, marked ease of fatigue and an elevation of pulse rate from 68 to 120. When thyroid was omitted these symptoms disappeared, the metabolism returned to minus 24 per cent, and the patient felt well again.

II. *Abnormal Persons*.—Of the 185 subjects who were abnormal, 36 were males and 149 were females. Their ages ranged from 10 to 70 years, with fairly even distribution for each decade from the second through the fifth, only six cases falling outside these limits. Although the symptoms, physical signs and basal metabolism were repeatedly observed, it was only in an occasional instance that any material improvement was noted following the administration of desiccated thyroid. None of these cases was typical of myxedema clinically, although they often showed a few symptoms that are also characteristic of that disorder, such as ease of fatigue.

A. *Nervous, Worrying Persons Who Become Fatigued Easily*: These patients, only 6 of whom were males, formed the largest group of the series. They presented the following clinical picture: The symptoms (listed in order of frequency) were lack of endurance, marked nervousness, marked tendency to worry and emotional upsets on slight provocation, sensitiveness to cold, numbness and tingling of extremities, constipation, headache, vague pains, dizziness, palpitation and often dyspnea on exertion.

The signs were as follows: The basal metabolic rate was below normal in all cases. Weight was normal in 49 per cent, less than average in 31 per cent, and more than average in 20 per cent of the cases. The systolic blood pressure was from 104 to 198 mm. of mercury and the diastolic pressure from 60 to 100 mm. of mercury. The pulse rate was below 76 beats per minute in 59 per cent and 76 beats per minute or above in 41 per cent. Catamenia was normal in 40 per cent of women and irregular (delayed and scanty) in 60 per cent of women. There were no changes in the hair, skin or nails.

In addition to showing a few symptoms also shown by patients with myxedema (notably ease of fatigue, and in some cases sensitiveness to cold and diminished catamenia), the clinical picture presented by these patients was similar in some respects to that in other conditions unassociated with a low metabolism. For example, marked nervousness on slight provocation, marked tachycardia on excitement and moderate exertion and lack of endurance are said to be outstanding symptoms in the patients with "mild hyperthyroidism" and slightly increased metabolism reported by Miller and Raulston.²² Dizziness, insomnia, fatigue, palpi-

22. Miller, J. L., and Raulston, B. O.: The Recognition of Mild Hyperthyroidism, J. A. M. A. **79**:1509 (Oct. 28) 1922.

13 per cent, and a second test was minus 21 per cent. Three grains (0.19 Gm.) of desiccated thyroid daily raised it to plus 2 per cent, without clinical improvement; that is to say, she continued to be easily fatigued, to have headaches and to be sensitive to cold.

A few of the other patients of this type to whom desiccated thyroid was administered felt a little better at times while taking it, but the improvement was short-lived. In most instances there was no change in symptoms.

B. Patients Whose Chief Complaint Was Diminished Menstruation: There were 21 patients who complained chiefly of diminished menstruation.²⁴ In the majority of instances it was delayed from two weeks to three months, and a few patients were observed who had amenorrhea for a year or more. Since amenorrhea may be associated with several pathologic conditions, this group probably contains more than one clinical entity. There were no outstanding characteristics that could be described, except that these patients were more frequently overweight than underweight and, as a rule, stronger and more active and suffered little from muscular fatigue as compared with the patients of group A. Nervousness, irritability and sensitiveness to cold were either not present or not marked. An example follows:

A. P. (figs. 3 and 4), a school girl, aged 15, came to the hospital complaining that her menstruation was delayed from one to two weeks. The only objective changes discernible were cool hands and feet, with the skin of the hands and arms slightly dry. She was of average intelligence and indulged in ordinary activities without undue fatigue. She was 10 Kg. overweight. The systolic blood pressure was 122 mm. of mercury and the diastolic pressure 74 mm. She did not appear myxedematous, although her basal metabolism dropped as low as minus 35 per cent. Desiccated thyroid in doses of 3 grains (0.19 Gm.) daily raised the metabolism from minus 26 per cent to normal without producing a significant change in her condition. A drop in metabolism occurred in conjunction with the oral administration of anterior pituitary extract in doses of 15 grains (0.97 Gm.) daily, and a restriction of diet to approximately basal requirements. There was no gross evidence of pituitary disease; that is to say, the fundi, spinal fluid and roentgenograms of the sella turcica showed no abnormalities, and the patient did not have headaches.

Another patient may be mentioned as of special interest:

C. S. (fig. 5), a schoolgirl, aged 15, first came to the clinic in November, 1928, complaining that she menstruated only every six to twelve weeks, and that she had gained 40 pounds (18.1 Kg.) in the preceding nine months. When first seen

24. As previously stated, irregularities of menstruation were not limited to this group. Considering the 196 cases as a whole, excessive menstruation was not present in any at the time of observation. There were 2 cases in which this was the original disorder, but a dilatation and curettage in both and roentgen treatment over the pelvis in one of them were followed by scanty and delayed catamenia.

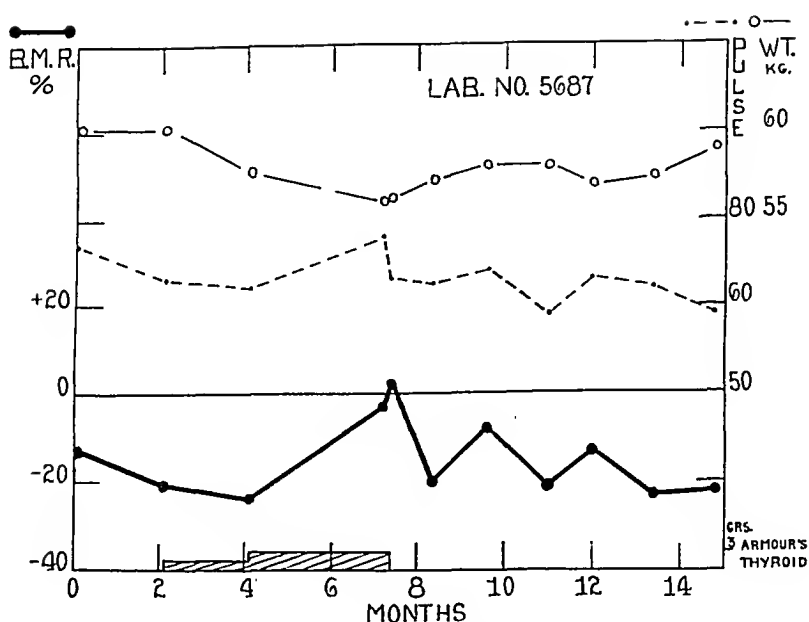


Fig. 1.—Chart showing low basal metabolism in a nervous worrying type of woman, aged 43, who had had severe headaches frequently since childhood and tired very easily. Three grains of desiccated thyroid daily produced no clinical improvement although the metabolism was raised to normal. (In this and subsequent figures, the cross-hatched areas denote periods of treatment with desiccated thyroid.)



Fig. 2.—Comparison of photograph of Mrs. A. T. on the left (taken Dec. 11, 1928, when the basal metabolic rate was minus 20 per cent) with that of a typical patient with myxedema (Mrs. M. V. L.) on the right of about the same age and with about the same depression of the basal metabolic rate.

in the clinic her weight was 27 pounds (12.2 Kg.) above the average for her height. Her appetite was large. She had had gonorrhea about two years previously, which caused an endocervicitis. There was a tendency toward masculine distribution of hair. The shape of her hands and feet and the distribution of body fat were not typical of a true Fröhlich syndrome. There was no puffiness of her face or eyelids, although the basal metabolism for the most part varied between minus 20 and minus 25 per cent. She was unusually active and did well in school in spite of little study. Numerous social activities caused little fatigue, and she required only an ordinary amount of sleep. She was said to be precocious sexually. The administration of 6 grains (0.46 Gm.) of desiccated thyroid daily raised her basal metabolism to only minus 12 per cent and produced no clinical change. Anterior pituitary tablets were likewise without effect.



Fig. 5.—Miss C. S., Feb. 5, 1929, with a basal metabolic rate of minus 20 per cent.

In other cases we have tried an ovarian substance, corpus luteum, and anterior pituitary, singly and in combinations, as well as raising the metabolism to standard normal by giving desiccated thyroid, without material amelioration of symptoms.

It would be important to know in how many such cases, if any, the primary disorder is an underfunction of the ovaries. Active ovarian preparations have not been available long enough to determine this.

C. Hypothyroidism Without Myxedema: There were 13 patients who appeared to have an underfunction of the thyroid but no detectable edema (possibly because the condition was so mild). The essential difference between this type of patient and the others who are classed

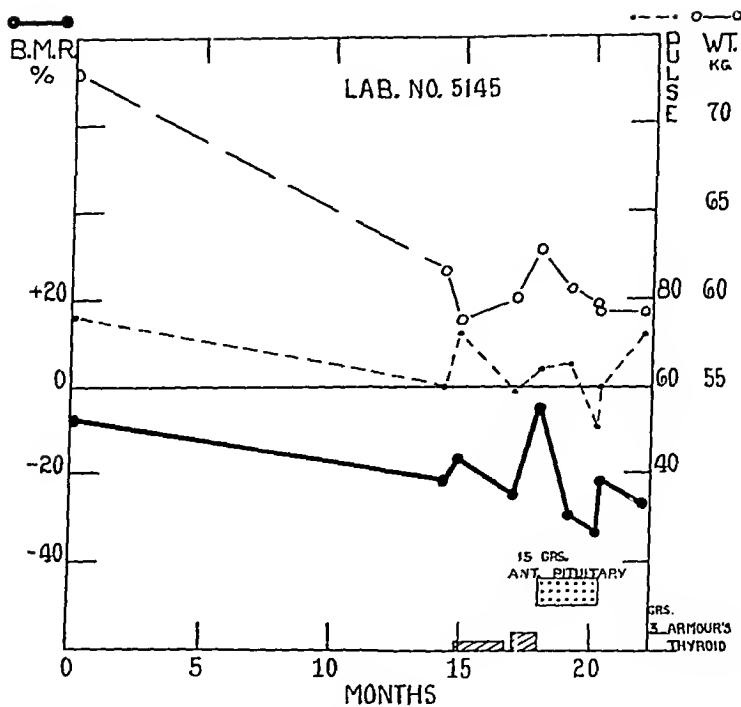


Fig. 3.—Chart showing marked depression of the basal metabolic rate in a girl, aged 15, in association with diminished catamenia and overweight, without any demonstrable underfunction of the thyroid. Three grains of desiccated thyroid daily produced no significant change except for some increase in metabolism. Loss of weight was associated with a decrease in the food intake.



Fig. 4.—Miss A. P., Dec. 20, 1928, with a basal metabolic rate of minus 16 per cent.

D. C. (fig. 7), a high school girl, aged 17, entered the medical service on Jan. 3, 1927), complaining of loss of appetite, weight and strength. She had been well until nine months before admission, when, largely because of the teasing of her companions about her "corpulence" and to some extent because her appetite was failing under the emotional stress of great scholastic effort, she began to diet. She had lost 22.7 Kg. in weight (weight on admission, 31.7 Kg.), was markedly asthenic and easily irritated by noises. Amenorrhea had been present for ten months. Physical examination showed extreme emaciation, dry scaly skin, and rather abundant fine hair over the entire body. The systolic blood pressure was 78 mm. of mercury and diastolic pressure 62 mm. The basal metabolism was minus 46 and minus 48 per cent on two occasions. At no time was she considered to be myxedematous. Through psychoanalysis and a gradually increasing diet, she improved, gained 10.8 Kg. and the basal

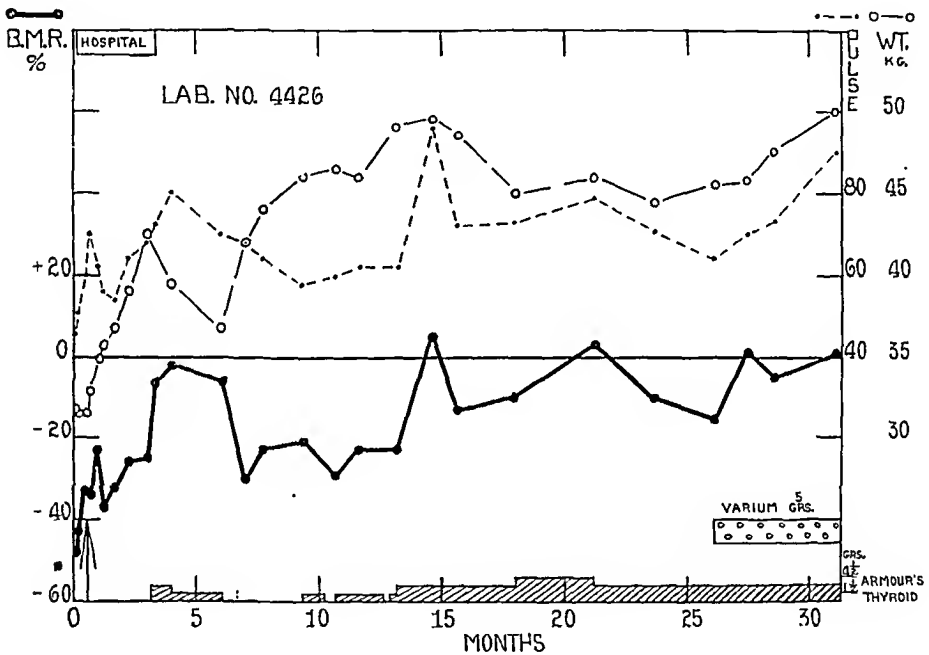


Fig. 7.—Chart showing the course of the weight and basal metabolic rate in a girl aged 17 during recovery from malnutrition.

metabolism rose to minus 25 per cent during the first three months of treatment. Desiccated thyroid in doses of $1\frac{1}{2}$ to 3 grains (0.097 to 0.195 Gm.) daily was then given and raised the metabolism still further to minus 2 per cent. On omitting thyroid, the metabolism fell to minus 30 per cent. While taking thyroid she seemed to be more lively, the skin became soft and warm, and the distribution of hair returned to normal, but the opposite changes did not occur when she omitted it. Up to the present time, i. e., thirty-two months after starting treatment, her menstruation has not returned. Whether the low metabolism that persisted after the gain in weight was caused by an underfunction of the thyroid or not, is uncertain. In any case, when her metabolism was raised to normal by thyroid she was by no means completely well, and still suffered from ease of fatigue and a poor appetite.

as having no underfunction of the thyroid was the striking clinical improvement noted in the former when the metabolism was raised to standard normal by the administration of desiccated thyroid, while the latter either experienced no change or suffered from thyroid intoxication. The following case is an example of the type with mild hypothyroidism but no myxedema:

F. S. (fig. 6), a high school senior, aged 16, was lively and vivacious up to two years before examination, when she became nervous, irritable, cried easily and experienced palpitation on exertion. Muscular fatigue, sensitiveness to cold weather and sleepiness during the day developed. Constipation was marked. Menstruation was always from two to eight weeks overdue. She perspired freely. The results of physical examination were negative except for slight pallor of the skin and the fact that she was 4 Kg. overweight. The systolic blood pressure was

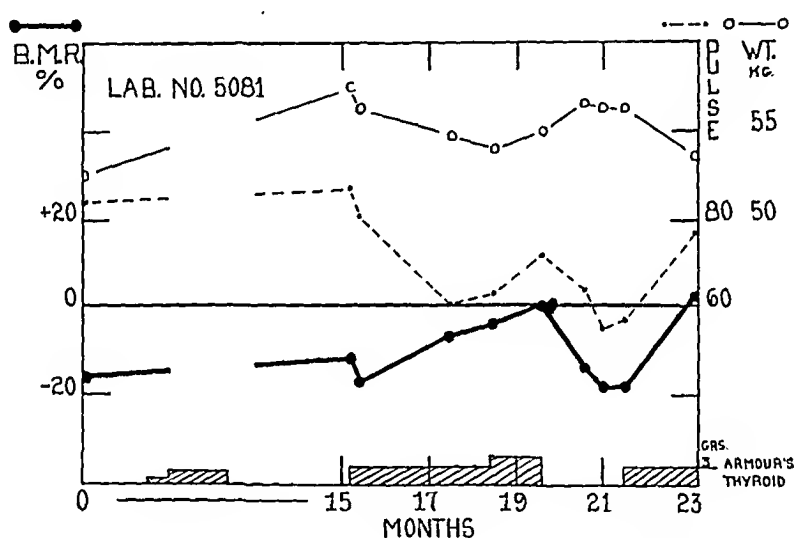


Fig. 6.—Chart showing hypothyroidism in a girl aged 16, without any detectable edema. Striking clinical improvement was noted during each administration of desiccated thyroid.

122 mm. of mercury and the diastolic pressure 94 mm. The basal metabolism ranged from minus 12 to minus 18 per cent. Desiccated thyroid in doses of 3 grains daily raised her metabolism to standard normal. She became more lively; her appetite increased; constipation and sensitiveness to cold disappeared, and her catamenia were more regular. On omitting thyroid for one month, the metabolism fell to a level of minus 18 per cent and all of her previous symptoms recurred.

D. Other Condition That Are Sometimes Associated With Low Basal Metabolism: The following cases are presented as clinical entities which have an associated low metabolism without clinical evidence of myxedema:

Malnutrition.—This case is one in which malnutrition was the associated condition.

R. L. (lab no. 5725), aged 19, a box toe sorter in a shoe factory, first entered the hospital in 1926 with muscular weakness and slight atrophy of the muscles of the arms, legs and abdomen, bilateral wrist and ankle drop, loss of position sense, paresthesia of the extremities and insomnia. His recovery was slow, but progressive. A diagnosis of multiple neuritis was made. He again entered the hospital on March 30, 1928, with a recurrence of all his former symptoms in more pronounced form than during the first attack. Muscular atrophy was striking and weakness was so marked that he could not walk. The basal metabolism was minus 18 and minus 21 per cent on two occasions. Again, recovery was gradual. Within six months muscle tone was regained, body weight increased 17.9 Kg. and the metabolism rose to plus 12 per cent.



Fig. 9.—Sisters, each of whom had a slight enlargement of the thyroid and a low basal metabolic rate without evidence of thyroid underfunction. On the left is Miss B. L., aged 14, with a basal metabolic rate of minus 20 per cent; on the right, Miss R. L., aged 17, with a basal metabolic rate of minus 14 per cent.

Colloid Goiter.—We have included in the miscellaneous group, 18 patients who had colloid goiter. The basal metabolisms ranged from minus 14 to minus 25 per cent. In none of them were we able to demonstrate by our criteria an underfunction of the thyroid (fig. 9). It therefore seems possible that they fall into some of the other classifications previously mentioned, in which an underfunction of the thyroid does not appear to be present.

The data are not extensive enough to permit the drawing of definite conclusions. They do show that a patient may have a low basal metabolism in the hospital and a normal one in the outpatient department, and that in making comparisons it is desirable to have all determinations done under the same conditions. To minimize the variables affecting basal metabolism, the determination in each subject in our series was repeated until a satisfactory level was obtained.

COMMENT

In this study we have considered it our most important problem to demonstrate the presence or absence of an underfunction of the thyroid gland. The criteria that we have used may be questioned, but we know of no better than clinical improvement when the basal metabolism is raised to standard normal by administering the appropriate dose of desiccated thyroid. Failure to improve under these conditions, or the production of thyroid intoxication, together with a clinical picture in the first place that was not characteristic of hypothyroidism, certainly must at least arouse the suspicion that some other condition may exist.

While there are many exceptions, the amount of edema in hypothyroidism is roughly proportional to the depression of the basal metabolism. It might naturally be supposed that all degrees of myxedema would be encountered in association with depression of the basal metabolism, varying from slight to marked. In general however, an underfunction of the thyroid is usually marked or else is absent, and a search for cases of hypothyroidism too mild to be myxedematous is not as fruitful as one would anticipate. The fact that only 13 such cases were discovered in this study serves to emphasize its rarity.

In the past there has been a tendency to attribute all low basal metabolism to an underfunction of the thyroid, and to consider this of two kinds: (1) primary, the result of direct injury to the thyroid gland; (2) secondary, the result of loss of the stimulus to the thyroid from some other gland of internal secretion, or a result of some other pathologic condition in which the thyroid suffers with the rest of the body, e. g., malnutrition. In other words, cases similar to those that we have described have been reported as cases of "hypothyroidism without myxedema" and "secondary hypothyroidism." We feel that it has been satisfactorily demonstrated that the first condition does exist and we think that the second condition probably exists, although we have not yet succeeded in demonstrating a case. The significant thing, however, is that both conditions appear to be rare in comparison with the large

VARIATION OF BASAL METABOLISM AND THE FACTOR OF REST

The conditions under which basal metabolism tests are done is of some importance. Except in a few instances, our subjects were outpatients. Some cases came from such a distance that two hours or more were required to reach the hospital. The effect of these rather long journeys on the basal metabolism would thus seem to be of interest.

In 20 cases (not necessarily those previously classified), observations were made on the same patient both after the usual half-hour's rest in the outpatient department and after a night's rest or longer in

TABLE 2.—*Comparison of the Basal Metabolism of the Same Person in the Outpatient Department and in the Hospital*

Patient	Laboratory Number	Average Basal Metabolic Rate in Outpatient Department, per Cent Normal	Average Basal Metabolic Rate in the Hospital, per Cent Normal	Difference, Points
Miss H. P.	5811	+ 1	-15	-16
Mrs. A. B.	4308	- 9	-22	-13
Mrs. M. O.	5013	- 8	-21	-13
Miss B. R.	4872	- 2	-15	-13
Miss D. B.	4701	- 7	-19	-12
Mr. E. T.	2259	-12	-24	-12
Miss S. H. C.	2181	- 5	-16	-11
Miss M. N.	4903	- 9	-18	- 9
Miss K. W.	5027	-10	-19	- 9
Miss M. G.	6516	-12	-21	- 9
Mr. N. P.	3142	- 8	-15	- 7
Mrs. E. McL.	4611	- 2	- 8	- 6
Miss M. V. M.	6460	-27	-32	- 5
Miss G. H.	5867	-12	-14	- 2
Miss C. S.	4133	- 8	-10	- 2
Miss J. K. A.	4664	- 8	-10	- 2
Miss M. McC.	3560	- 9	-10	- 1
Mrs. M. B.	6530	-35	-35	0
Mr. K. A.	3878	- 8	- 7	+ 1
Miss M. G.	6516	-18	- 6	+12
Average.....		-11	-17	- 6

the hospital. These observations are recorded in table 2. In 7 the metabolism was more than 10 per cent lower in the hospital, the maximum difference being 16 per cent. In 4 cases from fifteen months to five years elapsed from the time the determinations were made in the hospital until they were repeated in the outpatient department, thus rendering the value of the difference noted questionable. Three of these were among the 7 who showed a difference of more than 10 per cent. For all 20 cases the average basal metabolic rate in the outpatient department was minus 11 per cent, and in the hospital it was minus 17 per cent.

As previously stated, a large number of patients not included in this study had only one low rate among several normal ones. For example, one patient had 11 determinations, all of which were normal except for one of minus 17 per cent. The determination seemed to be reliable. Numerous similar situations were noted.

hemithyroidectomy on April 13, 1928. The day before the operation, the basal metabolism was minus 20 per cent. The left lobe of the thyroid is still readily palpable and the same pathologic condition probably exists in it as in the other lobe. Nevertheless, her basal metabolism has been unaffected by the operation and has been repeatedly observed at a level of minus 15 to minus 21 per cent over a period of fourteen months. She is an intelligent woman, has several normal children, and for years, in addition to looking after her own home, has done dressmaking to augment the family income. Raising the basal metabolism to normal with 3 grains of desiccated thyroid daily produced no clinical change. She has no edema, her skin and hair are soft and smooth, her weight and catamenia are normal. In other words, except for the pathologic condition of the thyroid and the low basal metabolism, the woman would be considered normal. A somewhat similar case has been referred to in another study.²⁵

To prove that the low metabolism was caused by the disease it must be shown either that the metabolism was normal just before the disease began, or that it returned to normal when the disease disappeared.

It is a matter of interest that most variations of the basal metabolism in the so-called normal zone of plus or minus 10 per cent are below the zero line rather than above. It is, therefore, possible that the lower limits of our standards are a little high. Du Bois²⁶ has recently said that the Aub-Du Bois standards are 6 per cent too high.

Perhaps three of the most outstanding facts about patients who have a basal metabolic rate of 15 to 25 per cent below the average (normal) are: (1) the large number of these persons, (2) no underfunction of the thyroid can be demonstrated in the majority of them and (3) most of them appear to be abnormal.

SUMMARY

Frequent observations have been made on 196 patients with basal metabolisms of 11 to 45 per cent below the average normal (in only 8 was it lower than minus 25 per cent), but no edema that could be detected.

At least 11 patients could be considered normal (with basal metabolic rates varying from minus 11 to minus 24 per cent), but it was often difficult to decide whether a patient was normal or abnormal.

In 13 there appeared to be an underfunction of the thyroid which was apparently too mild to result in myxedema (so-called "hypothyroidism without myxedema").

25. Thompson and Thompson (footnote 1, second reference, case 2).

26. Du Bois, E.: Communicated through Dr. Graham Lusk.

number of patients who have a depression of the basal metabolism but no thyroid underfunction.

If it is true that most of these patients have no hypothyroidism, the next problem is to discover what is the matter with them, for most of them appear to be abnormal. In this direction little progress has been made. It is possible that a careful clinical study of large groups of these patients will enable a more accurate clinical classification to be made, and perhaps furnish clues to the underlying abnormalities. It is our impression, however, that most light will be thrown on the subject as therapeutically active preparations of various glands of internal secretion become available, and the clinical syndromes associated with their absence in the body become well differentiated. For example, in a woman who is somewhat overweight and who has absent or scanty menstruation but no thyroid underfunction, it is difficult to tell whether the chief trouble is in the anterior lobe of the pituitary or in the ovary itself. The problem could soon be settled if active preparations of these organs were made. The field is comparatively large and new and will amply reward the diligent investigator. It would seem strange that with so many important glands of internal secretion in the body the thyroid should prove to be the only one that affects the consumption of oxygen.

There are, however, certain other conditions often associated with a low metabolism in which the primary fault is not underfunction of any gland of internal secretion, e. g., malnutrition (either the result of organic disease or experiment), many debilitating diseases and muscular atrophy. It can, of course, be argued that the low metabolism may result from secondary involvement of glands of internal secretion. The patient with multiple neuritis and muscular atrophy (with a metabolism of minus 22 per cent during the acute stage of his illness and a return of the metabolism to standard normal coincident with the regaining of muscle tone and recovery) is of interest. It seems highly probable that the chemical changes occurring in the large mass of muscles in the body are responsible for a considerable portion of the total metabolism. In any event, the question of the influence of muscle tone on metabolism is raised.

Low basal metabolism is not an uncommon observation in patients with colloid goiter and nontoxic adenomatous goiter. In the majority of such cases, no underfunction of the thyroid can be demonstrated, and in them it is probable that the low metabolism is caused by other factors. The mere association of a low basal metabolism with a disease is not evidence that the disease causes it, as the metabolism may have been low before its onset. In this connection a patient (lab. no. 5729) with chronic thyroiditis (Riedel's struma) is of interest. She had a right

Book Reviews

SOME ASPECTS OF THE CANCER PROBLEM. By W. BLAIR BELL. Price, \$20. Pp. 5500. New York: William Wood & Company, 1930.

This large volume is well printed and bound and lavishly illustrated. It is in large part simply a republication of a long series of papers published by the Liverpool Cancer Research organization. These papers are connected with a series of short notes by the editor, commenting on the purpose and the value of the work.

That portion of the work which leads up to the clinical treatment for cancer is of a high scientific caliber and represents studies in all the fields of medicine which the author believed would throw light on the problem of the origin of cancer and especially those studies which lead to treatment for cancer with lead salts.

In the clinical sections, however, the reader cannot but be left unimpressed with the results obtained. The last two papers by Bell and others will be discussed briefly, the results of the clinical work being summarized. In the first of these, 227 cases were studied, of which arrest or cure of the disease was claimed in 50. A number of case histories are summarized which are illustrative of the various groups given in the author's tables, but unfortunately he does not always state which group they are made to illustrate. However, of 13 cases given which are illustrative of cures, 3 patients, numbers 178, 185 and 177, were reported as still having palpable tumors. Three others, 18, 11 and 44, underwent operations for removal of the tumors, which the author claimed were incomplete but gave no histologic proof that a tumor was left behind. In number 129 there was a carcinoma of the esophagus; no microscopic examination was made. Thus one may, by cursory examination, rule out 7 of the 13 as having no possible value as scientific evidence.

In the next paper there is a summary of all the statistics. One finds that of 566 cases, 63 were arrested or cured. Here the data presented in the illustrative case reports are still more illuminating. Four of the patients treated by lead alone, numbers 39, 22, 53 and 25, had no microscopic evidences of carcinoma. More astounding still (case 102), a patient with carcinoma of the mouth had received 80 mg. of radium for twenty-four hours as a treatment less than two weeks before the first treatment with lead was begun! Again one comes to the group of 12 patients said to have had incomplete operations. It is so well known to modern pathologists that much of the indurated area surrounding ulcerated carcinoma is inflammatory and not neoplastic that evidence of this kind must be considered totally worthless. Another large group of cases consisted of recurrences of carcinoma which had previously been confirmed by section in which no section was made to prove that the recurrent growth was carcinoma. Two patients (numbers 110 and 216) were concurrently treated by both roentgen rays and radium. In number 161 the patient presented a shadow in the lung which was diagnosed carcinoma on roentgen evidence alone. In number 365 the patient had two operations as well as lead therapy for recurrent cancer of the skin of the breast. In number 173 a gland appeared in the neck after excision of the breast after carcinoma. This gland was not examined microscopically. Also included apparently in the cures attributed to lead are 29 cases in which the patients underwent operation plus lead therapy and 10 cases in which they received lead therapy plus roentgen treatment.

This brief analysis of the statistical evidence of the therapeutic value of lead shows clearly in the reviewers mind that so far, at least, the evidence presented amounts to practically zero. In as important and difficult a field as the evaluation of any form of therapy for cancer the presentation of such slipshod, incomplete evidence in which, in a large number of cured cases, cancer had not been proved and in a still greater number of which all the other weapons in the armamentarium of the profession had been applied, cannot be too strongly condemned.

The remaining 172 patients appeared to be suffering from various pathologic conditions but not from an underfunction of the thyroid, as judged by the clinical picture and the response to doses of desiccated thyroid sufficient to maintain the basal metabolism at a standard normal level.

An exact differentiation into clinical entities is not yet possible in a large number of these cases, but a rough classification has been made, largely on the basis of symptoms.

There were 79 in whom nervousness, worry and ease of fatigue were the outstanding complaints; 21 in whom scantiness or absence of menstruation was the outstanding abnormality; and 72 who suffered from various other pathologic conditions such as starvation, pituitary tumor and muscular atrophy.

Muscle tone appears to be an important factor in regulating the rate of oxygen consumption under basal conditions.

If the basal metabolism is lower than minus 25 per cent, an underfunction of the thyroid is usually present. If the depression is less than 21 per cent below the average normal, an underfunction of the thyroid is usually not present.

THE BASIS OF EPILEPSY. By EDWARD TRACY. Price, \$2. Boston: Richard G. Badger, 1930.

The author is convinced that epilepsy is due to a disturbance of the sympathetic nervous system. The whole basis for this argument lies in the fact that spontaneously there are small white spots found on the skin of epileptic patients, which he interprets as areas of vasoconstriction. By stroking the skin with a special instrument, the white vasoconstriction line is shown to be increased in intensity in epileptic patients. This excess vasoconstriction is evidence of a sympathetic hypertonia, which is due to an imbalance of the vasomotor reflexes. This is the author's only physiologic proof. His anatomic proof consists in references to Echeverria's "Anatomical Pathologic Studies on Epileptics" of 1870, at a period when neuropathologic conceptions were in their infancy. The author attempts to diagnose incipient epilepsy by the white spots. He gives numerous case reports containing many irrelevant observations. His conclusions are, as a whole, unwarranted.

CLINICAL EXAMINATION OF THE NERVOUS SYSTEM. By G. H. MONROD-KROHN, M.D., F.R.C.P. Price, \$2.50. New York: Paul B. Hoeber, Inc., 1930.

That this excellent book should have passed through five editions in the course of nine years would seem to be ample evidence of its value. It presents a careful detailed study of the examination of the entire nervous system, lucidly informing the reader how each step should be performed, the interpretation to be placed on the observations and the pit-falls to be avoided. The additions to this edition concerning ventriculography and encephalography are valuable addenda. The text is not concerned with the discussion of clinical or pathologic entities; this is a great advantage over other books on neurology as it lends to the brevity, conciseness and clearness which characterize this little volume. It should continue to find an important place among the books of the student of neurology and also the practitioner of general and specialized medicine.

LES URTICAIRES. By EDOUARD JOLTRAIN. Price, 40 francs. Pp. 417. Paris: Gaston Doin.

This small paper bound volume is devoted entirely to the clinical and theoretical study of urticaria, and therefore commends itself especially to those interested in this subject. The author, a former pupil of Widal, prefaces the work by an extensive and sympathetic biography of his teacher. The various physical and chemical causes of urticaria are considered in separate chapters. The author emphasizes urticaria caused by emotional shock and fatigue. A final chapter is devoted to the therapeutics of urticaria. A long list of general and local treatments are given, but it must be admitted that little is said concerning which of these are the treatments of choice.

Concluding this treatise is an extensive bibliography mainly referring to French literature. There are eight photographic illustrations accompanying the text.

DIE ARTEN DER SCHLAGANFALLE DES GEHIRNS UND IHRE ENTSTEHUNG. By DR. P. SCHWARTZ. Price, 48 marks. Berlin: Julius Springer.

Apoplexies are discussed under three headings: the hemorrhages associated with hypertension, the softening associated with arteriosclerosis and the embolic disorders. A thorough review of the literature is first given by the author. He then discusses the macroscopic localizations of the various types of lesions and shows how they are dependent on the blood supply of the various portions of the brain. The gross and microscopic appearances of the various lesions are described in great detail and the pathogenesis is then discussed. One hundred and fifty excellent illustrations graphically picture his work. The author has written a thorough and adequate description of the apoplexies, the numerous details of which must be studied by any one interested in the subject.

Coupled with the fact that lead therapy for cancer has received but little consideration after attempts at its use in a large number of other clinics, one cannot help but wonder what was the reason for the republication of all of this enormous mass of material at such great expense.

SYMPTOMS OF VISCERAL DISEASE. A STUDY OF THE VEGETATIVE NERVOUS SYSTEM IN ITS RELATIONSHIP TO CLINICAL MEDICINE. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Monrovia, Calif. Fourth edition. Price, \$7.50. Pp. 426, with 87 text illustrations and 10 color plates. St. Louis: C. V. Mosby Company.

The author of this work is a skilled clinician who has made a life-long study of the symptoms of disease and who consequently has been led into the maize of problems associated with visceral neurology. His clinical observations have been carefully and accurately made and are well presented. Visceral neurology is clearly described anatomically and is thoroughly considered from the physiologic and pharmacologic standpoints.

The introductory chapter consists of a plea for the general consideration of the diseased patient, the fact being emphasized that "there is not only a disease which has the patient but a patient who has the disease."

Part I begins with a discussion of the control of protoplasmic activities, and of the rôle of chemical, psychic, reflex and endocrine factors, and proceeds to a careful description of the anatomy of the vegetative nervous system. Its physiology is considered as is its pharmacology, the latter including the tests for sympathicotonia and parasympathicotonia. A chapter on the relationship of the ionic content and physical state of the cell to cell activity and nerve stimulation concludes this section.

In the second part of the book, the symptoms of disease are classified as those attributable to toxemia, those attributable to reflex causes and those attributable to the disease process itself. These are then discussed, the major part of the section being devoted to the symptoms of reflex origin and to their mode of production.

Part III describes the innervation of the important viscera with a clinical study of the more important viscerogenic reflexes. This detailed analysis, comprising almost half the book, begins with the esophagus, considers the abdominal viscera in turn and then considers the thoracic viscera, the blood vessels, the salivary glands, the pharynx, the larynx and the eye, the urogenital tract, the skin and, finally, the endocrine glands.

The correlation of symptoms with the known facts of visceral neurology is the especial task undertaken by the author. In part, the conclusions seem well proved; in part, they seem highly speculative, but in any event they are interesting. The book could be condensed a great deal by the elimination of needless repetition.

SINDROME DE OCLUSION CORONARIA. By ANTONIO BATTRO. Pp. 200. Buenos Aires: Elateneo librería científica y literaria, 1930.

While containing comparatively little original matter, this monograph of 200 pages is an excellent summary of the knowledge of coronary diseases. In the first section, the anatomy of the coronary vessels is carefully worked out and contains numerous good illustrations in color as well as roentgenograms of injected specimens of human hearts. The lack of overlap of the coronary fields is emphasized in the following chapter on the physiology of the coronary circulation and one describing the clinical symptoms of infarction of the myocardium. The best part of the work consists of a series of experimental studies, giving electrocardiograms of the cases in which the coronary vessels were ligated experimentally in various places. These are backed up by microscopic sections of the same material. The author continues with case reports, showing postmortem appearances together with the electrocardiographic tracings before death of a number of both acute and chronic cases. The work is well done and clearly written and contains an extensive bibliography.

The subject matter will be considered under two general headings:

1. The three fundamental retinal lesions in hypertension.
2. The ophthalmoscopic observations in the individual hypertensive and renal diseases.

THE THREE FUNDAMENTAL RETINAL LESIONS IN HYPERTENSION

In the older literature, as well as in many recent publications, Liebreich's⁵ term "albuminuric retinitis" is used as a generic designation for all the lesions of the retina, except for those due to closure of large vessels, that occur in patients with renal disease. However, in 1916, Moore² clearly differentiated the ophthalmoscopic picture produced by retinal arteriosclerosis from that which he termed "renal retinitis." More recently, he stated:

I believe the general feeling of ophthalmic surgeons is that a fundus which shows numerous cotton wool patches, with edema and perhaps a retinal detachment, implies, not a different stage of disease, but a disease of a different type than that which is implied by a fundus showing marked vascular change, with numerous flame-shaped hemorrhages, little edema, a star figure composed of discrete dots, and no cotton wool patches. It will, however, be agreed that there are many intermediate cases which it is impossible to classify along these lines.

Moore does not attempt to correlate these different retinal lesions with individual types of renal disease. On the other hand, Keith, Wagener and Kernohan, on the basis of extensive investigations, believe that they can often differentiate the retinal lesions in the severe cases of essential hypertension which they term malignant hypertension from those which occur in glomerulonephritis. They found the following:

In malignant hypertension the edema of the retina is less extensive and less dense, and there is little tendency to the formation of peripapillary snow-bank exudates. The hyperemia of the disk is in marked contrast to the anemia of the disk and the retina that is seen in the retinitis of nephritis. Sclerosis of the retinal arterioles is always present in malignant hypertension and is usually absent in chronic nephritis.

As a result of the investigation of the material reported in this paper, we have come to the conclusion that the traditional unitary conception of "albuminuric retinitis" should be discarded; it is of great diagnostic and prognostic importance to differentiate three ophthalmoscopic pictures that may appear in patients suffering with diseases characterized by arterial hypertension: 1. Retinal arteriosclerosis and arteriosclerotic retinopathy. 2. Malignant hypertensive neuroretinitis. 3. Choked disk due to increased intracranial pressure.

5. Liebreich: *Arch. f. Ophth.* 5:265, 1859.

THE DIFFERENTIATION AND SIGNIFICANCE OF CERTAIN OPHTHALMOSCOPIC PICTURES IN HYPERTENSIVE DISEASES *

ARTHUR M. FISHBERG, M.D.

AND

B. S. OPPENHEIMER, M.D.

NEW YORK

In the great attention that has been devoted in recent years to the hypertensive and renal diseases, ophthalmoscopic studies have not been neglected. Especially noteworthy in this regard are the investigations of Wagener and Keith and their co-workers¹ on the retinal changes in what they term malignant hypertension, of Moore² and O'Hare and Walker³ on arteriosclerosis of the retina and of Volhard⁴ on the pathogenesis of the retinal process. In the present communication, we shall report the results of studies on the correlation of the ophthalmoscopic observations with the individual renal and hypertensive diseases.

The material comprises studies of the patients with arterial hypertension and the nonhypertensive forms of "Bright's disease" admitted to Mount Sinai Hospital during 1928 and 1929. All cases were discarded in which the diagnosis did not seem clear clinically or was not checked at necropsy, as well as those instances in which adequate ophthalmoscopic studies were not made. There remained 274 cases, on which the figures given in this paper are based. Thirty-nine of the cases were also studied at necropsy. In addition, we have utilized a number of cases observed in Mount Sinai Hospital during other years, as well as some from Montefiore Hospital; these, however, have not been included in the statistics.

* Submitted for publication, May 19, 1930.

* From the Medical Services of Mount Sinai and Montefiore Hospitals.

1. Wagener, H. P.: *Tr. Am. Ophth. Soc.* **25**:349, 1927. Keith, Norman M.; Wagener, Henry P., and Kernohan, James W.: *Syndrome of Malignant Hypertension*, *Arch. Int. Med.* **41**:141 (Feb.) 1928.

2. Moore: *Quart. J. Med.* **10**:29, 1916; *Medical Ophthalmology*, ed. 2, London, J. & A. Churchill, 1925.

3. O'Hare, J. P., and Walker, W. G.: *Arteriosclerosis*, *Arch. Int. Med.* **33**:343 (March) 1924.

4. Volhard: *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **33**:422, 1921.

profusely. Most often, the individual opacities are of small size; when such small spots are numerous, they give the "powdery" appearance. In other cases, they are large. When large, they often appear shiny, and their outlines are sharply delimited from the adjacent retina ("hard"), thus differentiating them from the "cotton-wool" patches found in malignant hypertensive neuroretinitis. The lesions may be white, yellowish or ivory-colored. Rather exceptionally, the spots may form a stellate figure around the macula or may have an irregular circinate arrangement in this region. Evidences of choroidal sclerosis with pigment changes are often present.

While retinal arteriosclerosis, as far as we have observed, is always bilateral, though often of greatly different intensity in the two eyes, the changes in the retina are not uncommonly unilateral for a long time. The picture may change strikingly from time to time. This is most often due to hemorrhages appearing or clearing up. But the white spots may also come and go; in a recent case they disappeared completely on two occasions.

As mentioned, this retinal picture is to be regarded as due to arteriosclerosis of the retinal arteries. When well marked, it is found only where hypertension has existed for a considerable time,⁷ and almost always other evidences of marked arteriosclerosis can be found in the larger vessels of one region or another (extremities, aorta, coronaries, cerebral arteries, etc.). The large majority of cases in which the picture occurs are those of essential hypertension. But we have also seen a considerable number of examples in glomerulonephritis of many years' duration. We have also observed the typical picture in a patient with hypertension due to amyloid contracted kidney. Particularly exquisite examples of the arteriosclerotic fundus are to be found in patients suffering from both diabetes and essential hypertension; the condition in these cases constitutes the so-called diabetic retinitis. According to

7. In accordance with the observations of O'Hare and Walker,³ we have found that marked retinal arteriosclerosis is practically pathognomonic of hypertension, either manifest or preexistent. In those cases in which we have noted marked retinal arteriosclerosis in the presence of normal blood pressure, there was cardiac enlargement or other evidence that hypertension had previously existed; as a rule, the disappearance of the hypertension was due to coronary artery disease. In a series of fifteen old patients who had marked arteriosclerosis of the radial and other large accessible arteries ("senile" arteriosclerosis) without any evidences that hypertension had ever been present, signs of retinal arteriosclerosis were either absent or but slight. The most frequent change in the retinal arteries of these patients was moderate thinning of the blood columns. The opportunity of examining some of these arteriosclerotic patients without evidence of hypertension, past or present, was given to us by Dr. Frederick D. Zeman and Dr. Robert K. Lambert.

RETINAL ARTERIOSCLEROSIS AND ARTERIOSCLEROTIC RETINOPATHY

In this group the changes in the fundus are the result of retinal arteriosclerosis. The retinal arteries show the characteristics of more or less marked arteriosclerosis, namely, irregularity of lumen, so-called arteriovenous compression, irregular light reflex, copper-colored appearance, white lines accompanying the blood columns ("perivasculitis"), etc. Generally, some constriction of the arteries, particularly of the smaller branches, can be made out, but this is, as a rule, not nearly as marked as in malignant hypertensive neuroretinitis. Increased tortuosity and a brilliant light reflex are often also considered as signs of arteriosclerosis, but their significance is difficult to evaluate. It should be pointed out that "arteriovenous compression," which is generally not actual compression but displacement of the vein by the artery passing over it into deeper portions of the retina, is not necessarily a sign of retinal arteriosclerosis but may be present in marked form merely as a manifestation of hypertension. This is proved by the fact that it is sometimes observed in cases of acute glomerulonephritis and hypertensive toxemia of pregnancy before there is time for the development of sclerosis. Possibly, the mechanism in such cases is that the artery with high blood pressure is more rigid than the normal vessel, much as a rubber tube becomes more rigid if fluid is forced through it under high pressure. In other cases, however, the venous compression is a direct consequence of the arteriosclerosis, for Friedenwald^{5a} found "actual encroachment of the thickened arterial and venous walls upon the common space within the common arteriovenous fibrous coat at the point of crossing." Evidences of retinal phlebosclerosis may also be present, and the veins may be distended, particularly if there is cardiac insufficiency.

The disk shows no abnormalities in most instances; in others, there is slight haziness of the outlines. In far advanced cases, there may be atrophic changes. The absence of papilledema is the most important criterion for differentiation from malignant hypertensive neuroretinitis.

The retina may not be demonstrably altered despite marked arteriosclerosis, or the changes may be extensive. Hemorrhages are often present. They may be single or multiple, large or small, superficial or deep, with or without relation to the larger vessels. White spots ("exudates")⁶ may be absent or present either in small numbers or

5a. Friedenwald: *The Pathology of the Eye*, New York, The Macmillan Company, 1929, p. 170.

6. The almost universal use of the word "exudate" as a general term for white and yellowish areas in the fundus in hypertensive diseases is unfortunate. Such areas are most often not manifestations of exudation, but result from degenerative or proliferative processes.

In some instances, well marked changes (exudate and hemorrhages) may appear in the retina before the papilledema. These cases are rather exceptional, and the papilledema is generally not long in making its appearance.

In the retina, hemorrhages are generally, though not always, present; they are of various sizes and shapes and may be either deep or superficial. White spots are usually also present. Contrary to those found in the arteriosclerotic retina, these opacities are most often of the soft, indistinctly bordered type often described as "cotton-wool." They may be very large and numerous and may merge so as to form an extensive peripapillary ring or cover practically the entire central retina. "Hard," sharply delimited opacities, the type seen in the arteriosclerotic retina, are often also present and in prolonged cases tend largely to replace the cotton-wool areas. A stellate figure may be formed about the macula.

The arterial blood columns are narrowed, generally to a striking and sometimes to an extreme degree. The degree of narrowing of different vessels varies in many instances. The narrowing of the arterial blood columns is, as far as we have observed, the first change in the ophthalmoscopic picture that later develops the features just described. However, marked narrowing of the retinal arteries may exist in hypertensive patients for long periods, as we have repeatedly observed, without the appearance of changes in the disk or the retina. There can be no doubt that the narrowing of the arterial blood columns is the result of functional vasoconstriction of the musculature of the retinal arteries, for it may appear early in the course of acute glomerulonephritis or the hypertensive toxemia of pregnancy before there is any opportunity for narrowing of the lumen by a proliferative process.

Arteriosclerosis of the retinal arteries may or may not accompany this form of retinal lesion. In long-standing cases of essential hypertension or chronic glomerulonephritis, evidences of arteriosclerosis are generally present and may be marked. On the other hand, if the retinal lesions occur in hypertension of relatively recent inception, as in the toxemia of pregnancy, the early stages of glomerulonephritis, or often in the malignant forms of essential hypertension in young persons, retinal arteriosclerosis is absent. The veins are generally distended, particularly when there is marked papilledema.

Malignant hypertensive neuroretinitis occurs in glomerulonephritis and essential hypertension; details of this occurrence and its significance are given in the following sections. It is present frequently in the hypertensive toxemia of pregnancy with or without eclampsia gravidarum. It also may appear in lead poisoning with hypertension; this

the description given by Duckworth,⁸ gouty retinitis (with which we have no personal experience) is apparently of this type, for he described hemorrhages as the outstanding feature in the presence of "small" arteries and the absence of optic neuritis.

The significance of arteriosclerotic retinopathy, severe though the changes in the retina may be, is purely that of arteriosclerosis. It does not necessarily indicate, as does malignant hypertensive neuroretinitis, that renal insufficiency either is present or threatens almost inevitably. The large majority of our patients with arteriosclerotic retinopathy who have died—they may live for many years with these retinal changes—have not succumbed to renal insufficiency but to cardiac failure, coronary closures, cerebral vascular disease, etc. When renal insufficiency does appear in patients with arteriosclerotic fundi, it tends to be less rapidly progressive than in those with malignant hypertensive neuroretinitis.

MALIGNANT HYPERTENSIVE NEURORETINITIS

This variety of retinal change is of much more ominous prognostic significance than the arteriosclerotic retinal lesions just described. It is characterized by the presence, generally though not invariably from the onset, of papilledema in addition to the retinal lesions. In view of this fact and the serious prognostic significance, it may be termed malignant hypertensive neuroretinitis.

As a rule, the appearance of papilledema is the first change in the fundus (apart from the usually antecedent constriction of the arteries), though most cases are first observed when retinal lesions are also present. In several instances that we have seen, the presence, alone or predominantly, of papilledema led to the suspicion of tumor of the brain. In most of our cases, the elevation of the disk was not notable, but Keith, Wagener and Kernohan, and Larsson⁹ described an elevation of as much as 6 diopters. As a rule, the presence of peripapillary edema and the consequent absence of abrupt transition make estimation of the elevation difficult or impossible. (Larsson carried out his measurements with the Gullstrand ophthalmoscope, which we have not used.) In most instances of essential hypertension with papilledema, the disk is reddened, but if there is also marked anemia, which occurs most often in glomerulonephritis, but also in the terminal uremia of essential hypertension, the disk may be very pale. In unusual cases of long standing, atrophy of the nerve finally supervenes.

8. Duckworth: *A Treatise on Gout*, Philadelphia, P. Blakiston's Son & Company, 1889, p. 94.

9. Larsson, S. W.: *Acta ophth.* 1:193, 1924.

urea nitrogen content of the blood was 11.9 mg. per hundred cubic centimeters. Albuminuria was generally, though not always, present while casts were seen only occasionally.

The ophthalmoscopic observations were as follows: In the right eye the nerve head was red; its margins were indistinct. The veins were engorged, the arteries extremely narrow and in places lost. There was perivasculitis. The left eye was the same as the right eye, but there were numerous fine spots of degeneration between the nerve head and the macula and a few larger white areas near the nerve head.

The symptomatology in the hospital was that of progressive myocardial insufficiency. The patient was subsequently transferred to Montefiore Hospital, where he developed bronchopneumonia; he died on March 27.

At necropsy the heart was found to be enormously hypertrophied and dilated (weight, 880 Gm.), the left ventricle being most affected. There were only slight changes in the kidneys. There was a hypernephroma of the right suprarenal gland and multiple adenomas of the left suprarenal gland. Further details of the clinical and anatomic observations will be found in our previous paper.

A similar case has since been reported by Winkel.¹⁴

On the other hand, renal insufficiency in glomerulonephritis, urinary obstruction and other conditions may be present for a long time and terminate in fatal uremia without retinal lesions. For these reasons, it seems clear that renal insufficiency in itself does not cause the retinal lesions.

Retinal Arteriosclerosis.—Von Michel¹⁵ and other earlier investigators considered "albuminuric retinitis" to be due to retinal arteriosclerosis. It is true that retinal arteriosclerosis does cause lesions of the retina, but this type, as we have seen, is to be differentiated from the type of retinal change considered in this section. In these cases, which we term malignant hypertensive neuroretinitis, retinal arteriosclerosis and its consequences may be present if there has been hypertension for a long time; in instances in which the hypertension is of brief duration, arteriosclerosis is absent. Anatomic demonstrations of this fact have been given by Schieck¹⁶ and others. That arteriosclerosis cannot be incriminated in the pathogenesis of the retinal process in acute glomerulonephritis or the toxemia of pregnancy is obvious.

It will be pointed out that in all cases of malignant hypertensive retinitis in essential hypertension that we were able to study at necropsy, necrosis of the renal arterioles was present. Whether a similar necrotizing process occurs in the retinal arterioles and contributes to the retinal mischief, we are unable to say. In a few sections of eyes in our cases that we have seen through the courtesy of Dr. I. Goldstein and Dr. D.

14. Winkel, M.: *Deutsches Arch. f. klin. Med.* **159**:1, 1928.

15. von Michel: *Ztschr. f. Augenh.* **2**:1, 1899.

16. Schieck: *Ber. ü. d. Versamml. d. 34 deutsch. ophth. Gesellsch.* 1907, p. 77.

may occur in the absence of renal involvement (Oliver,¹⁰ De Schweinitz¹¹). Finally, we¹² have observed it in a case of hypertension due to suprarenal tumor in which the kidneys were healthy.

PATHOGENESIS

In the efforts to clear up the pathogenesis of "albuminuric retinitis," attempts have been made to correlate the retinal lesions with five different manifestations of Bright's disease:

1. Renal insufficiency.
2. Retinal arteriosclerosis.
3. Increased intracranial pressure.
4. Hypercholesterolemia.
5. Arterial hypertension.

Renal Insufficiency.—Most of the early investigators believed the retinal lesions to be a consequence of renal insufficiency, the resulting abnormalities in the composition of the blood causing the retinal changes. Later, Vidal, Morax and Weill¹³ attributed the retinal changes to retained products of protein metabolism, for they found nitrogen retention in each of seventeen patients with retinal changes. However, this theory is entirely untenable, for retinal lesions of even extreme severity may occur in the presence of intact renal function; as Keith and his co-workers have emphasized, this occurs especially in essential hypertension, but we have also seen it in glomerulonephritis. In fact, malignant hypertensive neuroretinitis may occur in the presence of anatomically intact kidneys, as we observed in a case of hypertension resulting from suprarenal tumor. Because of the great theoretical importance for the pathogenesis of neuroretinitis in hypertensive disease of this case, which we¹² have reported in detail from another point of view, the salient features will be mentioned here.

CASE 1.—A man, aged 24, was admitted to Mount Sinai Hospital on Jan. 11, 1923. He had suffered from dyspnea on exertion and palpitation for three months. There were also precordial pain and a dry cough.

The patient breathed rapidly and with obvious effort. His heart was enlarged to the left and the right; a presystolic gallop rhythm was heard. The radial artery felt thickened; the blood pressure was 200 systolic and 150 diastolic. Pulsus alternans was present. There was no evidence of impairment of renal function; the specific gravity of the urine reached 1.025, and six days before death, the

10. Oliver, in Allbutt's System of Medicine, New York, The Macmillan Company, 1898, vol. 2, p. 973.

11. de Schweinitz: Toxic Amblyopias, Philadelphia, Lea Brothers & Company, 1896, p. 126.

12. Oppenheimer, B. S., and Fishberg, A. M.: Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

13. Vidal, Morax and Weill: Ann. d'ocul. **143**:354, 1910.

have borne out this observation. We have never seen an instance of so-called albuminuric retinitis in which there was not evidence of hypertension, past or present. Rarely, one encounters a patient with typical retinal changes in whom the blood pressure at the time of observation is not elevated. The instances of this variety that we have seen have been of two kinds: 1. The blood pressure has fallen in the terminal stages of uremia or as a result of disease of the coronary arteries. 2. In rare instances in children the retinal changes may occur with a relatively moderate hypertension, which is, in fact, proved to be hypertension only by the subsequent course of the case. Thus, in one such case in a child of 10 years, the blood pressure was only 124 systolic and 86 diastolic, but after recovery it was 95 systolic and 55 diastolic.

Not only is hypertension present in every instance of "albuminuric retinitis," but invariably, as far as we are aware, it precedes the appearance of the retinal lesions. As yet unsolved, however, is the problem of the nature of the connection between arterial hypertension and the retinal process. Why is hypertension present in a maximal degree in many cases without affecting the retina, while in other cases it induces only arteriosclerotic changes in the retina, and in still others the malignant hypertensive neuroretinitis here under discussion? Volhard⁴ advanced the theory that the retinal lesions are manifestations of ischemia of the retina produced by a spasm of the retinal arteries which is part of the widespread vasoconstriction that is present in arterial hypertension. Among the evidence in favor of this theory are the following facts:

It was pointed out long ago by Gowers²⁰ that in hypertension the arterial blood columns in the retina are often narrowed. This is particularly marked, in fact often extreme, when malignant hypertensive neuroretinitis is present.

A number of observers (Elschnig,²¹ Wagenmann,²² Labadie-Lagrave and Laubry²³ and others) have observed spasms of the retinal arteries in hypertensive states. Recently, Haselhorst and Mylius²⁴ not only observed but photographed cramplike and rapidly changing contractions of the retinal arteries in a patient with eclampsia gravidarum. After two days the contractions became more constant and involved longer stretches of the arteries. At this time the first white degenerative lesions in the retina appeared.

20. Gowers: *Brit. M. J.* **2**:743, 1876.

21. Elschnig: *Wien. med. Wchnschr.* **48**:1305, 1898.

22. Wagenmann: *Arch. f. Ophth.* **43**:219, 1897.

23. Labadie-Lagrave and Laubry: *Tribuna méd.* **38**:437, 1906.

24. Haselhorst, G., and Mylius, K.: *Zentralbl. f. Gynäk.* **52**:1180, 1928.

Wexler, necrosis of the retinal or choroidal arterioles was not present. The question is being studied by Dr. Goldstein and Dr. Wexler, who will report their results.

Endarteritic lesions of the retinal and choroidal arteries, characterized by endothelial proliferation, are often, though not always, present in malignant hypertensive neuroretinitis. But they are too inconstant to be regarded as the primary cause of the lesions, and it is possible that they are secondary to the retinal process.

Increased Intracranial Pressure.—Cushing and Bordley¹⁷ described a remarkable case of chronic renal disease with severe retinal lesions in which the intracranial tension was so enormously increased that subtemporal decompression was carried out. Larsson⁹ found increased intrathecal pressure in each of eleven patients with hypertensive neuroretinitis, and expressed the belief that it may play a rôle in the pathogenesis of the lesion. However, increase in the cerebrospinal tension is present in only some of the patients with hypertensive neuroretinitis; in others, despite marked swelling of the disk and severe retinal lesions, as we have repeatedly observed, the intracranial tension is within normal limits and cannot be concerned in the pathogenesis of the retinal changes. However, there are instances of hypertensive disease in which edema of the brain does produce enormous increase in intracranial pressure and consequent choked disk; such cases form a class apart and will be considered in the subsequent material.

Hypercholesterolemia.—Because cholesterol esters are present in large quantities in many of the white lesions of the retina and because of the occurrence of hypercholesterolemia in some varieties of renal disease, Chauffard¹⁸ advanced the hypothesis that hypercholesterolemia is the cause of the retinal lesions. However, this hypothesis is not of general validity, for in the large majority of instances of essential hypertension or chronic glomerulonephritis of many years' standing with retinal lesions, hypercholesterolemia is absent. In chronic nephrosis in which hypercholesterolemia is generally marked, the retinal changes do not occur. It is possible, however, that when retinal lesions occur in subacute or early chronic glomerulonephritis, the presence of hypercholesterolemia may result in increased deposition of cholesterol in the retinal plaques.

Arterial Hypertension.—It was pointed out by Traube,¹⁹ in 1861, that retinal lesions occur only in those forms of renal disease in which there is hypertrophy of the left ventricle. All subsequent observations

17. Cushing and Bordley: *Am. J. M. Sc.* **136**:484, 1908.

18. Chauffard; Font-Reaul and Laroche: *Compt. rend. Soc. de biol.* **73**:283, 1912.

19. Traube: *Gesammelte Beiträge* **2**:985, 1870.

nephritis. Any dividing line between the two groups is of necessity purely arbitrary. We have included in the class of acute and subacute glomerulonephritis the cases of five months' or less duration when the patient is first admitted to the hospital. This time was chosen, because when glomerulonephritis has lasted half a year or more, the chances of complete recovery are rather small, and the term "chronic glomerulonephritis" conveys the notion of little likelihood of restitutio ad integrum.

ACUTE AND SUBACUTE GLOMERULONEPHRITIS

There were twenty-seven cases of this variety, in twenty-one of which arterial hypertension was demonstrated during the stay in the hospital. Of the twenty-seven cases, severe ophthalmoscopic changes were present in only two. In one of these the picture was typical of malignant hypertensive neuroretinitis, and the patient, a boy aged 14, died within two months of the appearance of the retinal lesions. The other patient was a child, aged 10, with glomerulonephritis, who developed papilledema with an elevation of 1.5 diopters and flame-shaped hemorrhages in the retina; the process was evidently of the nature of a beginning choked disk due to increased intracranial pressure, for it was accompanied by the Babinski sign and other evidences of cerebral implication. In eight other cases of acute and subacute glomerulonephritis, there were slight ophthalmoscopic abnormalities, either haziness of the papilla or constriction of the arteries, or both. In one instance there was considerable diffuse edema of the retina.

These observations are in accord with the general experience that severe changes in the fundus occur in only a small proportion of cases of recent glomerulonephritis. The small incidence of severe retinal lesions in acute glomerulonephritis is probably correlated with the fact that hypertension, the pathogenic factor underlying the retinal lesions, is marked and persistent in only a small part of the cases, though present at one time or another in the large majority of instances. Slight changes, notably narrowing of the arteries or haziness of the disk, are found in a considerable proportion of the cases, particularly if the fundus is examined repeatedly. They have no especial prognostic significance. The same is true of the occasional small hemorrhages that are found in the fundi; they may be present in the absence of notable hypertension and are apparently akin to the purpuric spots in the skin that are not uncommon in acute glomerulonephritis.

It is important from prognostic and therapeutic points of view that the ophthalmoscopic picture of malignant hypertensive retinitis be differentiated from the choked disk that results from edema of the brain. The presence of the latter conveys no implication as to the likelihood of

Ophthalmoscopic pictures similar to that of "albuminuric retinitis," even including the stellate figure about the macula, have been observed in the anemia of chlorosis, with improvement after disappearance of the anemia (de Schweinitz,²⁵ Augstein²⁶).

As a result of the circulatory disturbance in the retina produced by increased intracranial tension (e. g., in tumors of the brain with choked disk), changes may appear in the retina indistinguishable from those of malignant hypertensive neuroretinitis.

In view of these facts, it would seem that Volhard's theory that "albuminuric retinitis" is due to ischemia of the retina resulting from spastic contraction of the retinal arteries is deserving of serious consideration, although it cannot by any means be considered as established.

CHOKED DISK DUE TO EDEMA OF THE BRAIN

In hypertensive states, as a result of circulatory disturbances in the brain correlated with the hypertension (Oppenheimer and Fishberg²⁷), edema of the brain may develop, with a resultant increase in intracranial pressure. The manifestations of increased intracranial pressure—headache, nausea, vomiting, convulsions, choked disk, high pressure of the cerebrospinal fluid, etc.—may so dominate the clinical picture that a diagnosis of tumor of the brain is made, as has occurred several times in our experience.

Cases of choked disk due to edema of the brain in hypertensive states have been described by Cushing and Bordley,¹⁷ Volhard,⁴ Blackfan and Hamilton²⁸ and others. We have seen several such cases. They occur in glomerulonephritis, the hypertensive toxemia of pregnancy (eclampsia gravidarum) and, judging by the literature, lead encephalopathy. We have not encountered this syndrome in essential hypertension. As previously mentioned, the choked disk may be accompanied by changes in the retina appearing identical with those of malignant hypertensive neuroretinitis.

OPHTHALMOSCOPIC OBSERVATIONS IN THE INDIVIDUAL HYPERTENSIVE AND RENAL DISEASES

THE FUNDUS IN GLOMERULONEPHRITIS

The cases of glomerulonephritis are considered in two groups, one including the acute and subacute cases, and the other chronic glomerulo-

25. de Schweinitz: *Diseases of the Eye*, ed. 10, Philadelphia, W. B. Saunders Company, 1910, p. 499.

26. Augstein: *Klin. Monatsbl. f. Augenh.* **63**:174, 1919.

27. Oppenheimer, B. S., and Fishberg, A. M.: *Hypertensive Encephalopathy*, *Arch. Int. Med.* **41**:264 (Feb.) 1928.

28. Blackfan, K. D., and Hamilton, B.: *Boston M. & S. J.* **193**:617, 1925.

In the cases of chronic glomerulonephritis of the so-called nephrotic type, i. e., those cases in which the clinical picture is dominated by intense albuminuria and edema in the absence of more than slight hypertension, the fundus exhibits no change. In a high proportion of cases of chronic glomerulonephritis in children hypertension is long absent and so are retinal lesions. The same is true of subacute bacterial endocarditis which is often complicated, particularly in the bacteria-free stage, by glomerulonephritis. Finally, when chronic glomerulonephritis occurs in a tuberculous person, it is rarely marked by either hypertension or retinal lesions; in one such case in the foregoing series, the glomerulonephritis was present for years and was finally terminated by death from uremia, but neither hypertension nor retinal lesions ever developed.

Five of the patients suffering from chronic glomerulonephritis who had normal fundi died. Four of the deaths were from uremia, illustrating the long known fact that glomerulonephritis can progress to renal insufficiency and fatal uremia without the development of retinal lesions. However, such cases are much outnumbered by those with retinal lesions (table 1).

Retinal Arteriosclerosis and Arteriosclerotic Retinopathy.—In eight of the cases of chronic glomerulonephritis retinal arteriosclerosis was the only ophthalmoscopic observation, and in six others, the retinal arteriosclerosis was accompanied by the retinal changes which we described as arteriosclerotic retinopathy. Retinal arteriosclerosis and its consequences were also present in some of the patients who had malignant hypertensive retinitis, but these instances are considered with the latter change. In all instances of glomerulonephritis with retinal arteriosclerosis, the renal disease had been present for some years, in several for many years. Moore mentioned a case in which retinal arteriosclerosis developed within a few months; no such instances were included in our cases. All of the patients with retinal arteriosclerosis had diastolic blood pressures of over 100 mm. (table 1). The ophthalmoscopic pictures were the same as those seen when retinal arteriosclerosis or arteriosclerotic retinopathy occurs in essential hypertension. In the cases that came to necropsy, the glomerulonephritis was accompanied by arteriolo-sclerosis and usually by marked general arteriosclerosis; as is the case in essential hypertension, the retinal arteriosclerosis is but one manifestation of the injury to the arteries, and particularly of the arterioles, wrought by long-standing hypertension. The following case illustrates arteriosclerotic retinopathy occurring in chronic glomerulonephritis.

CASE 2.—A man, aged 38, was admitted to the hospital in a state of uremic coma. He had been ill with anasarca and suppression of urine at the age of 7

the appearance of renal insufficiency, and if the patient can be tided over the acute cerebral episode, complete recovery often follows. On the other hand, the appearance of true malignant hypertensive neuroretinitis in acute glomerulonephritis is of ominous prognostic significance; most such cases go on to renal insufficiency and uremia, though occasionally improvement and even recovery occur.

CHRONIC GLOMERULONEPHRITIS

Fifty-five cases of glomerulonephritis of more than five months' duration were studied. The large majority of the cases were of a duration of a number of years; in most of these long-standing cases it was impossible to determine even approximately the time of onset.

The direct correlation between arterial hypertension and retinal lesions in these fifty-five instances of chronic glomerulonephritis is immediately obvious from table 1.

TABLE 1.—*Chronic Glomerulonephritis*

	Number Cases	Number Cases with Diastolic Pressure Over 100 Mm.	Number Deaths While in Hospital
Negative fundus	24	7	5
Retinal arteriosclerosis	8	8	0
Arteriosclerotic retinopathy	6	6	3
Malignant hypertensive retinopathy.....	17	15*	11

* The two patients with malignant hypertensive retinitis in whom the diastolic blood pressure was under 100 mm. were admitted to the hospital shortly before death; in both instances, left ventricular hypertrophy was found at necropsy, demonstrating that hypertension had existed.

The fundus in chronic glomerulonephritis will be treated under the following headings:

Normal Fundus.—In twenty-four of the patients with chronic glomerulonephritis significant changes in the fundus were not observed. In this group are included several instances in which narrowing of the arteries or haziness of the margins of the disks was noted, but which progressed no further during the period of observation. As table 1 shows, most of the patients with negative fundi had no hypertension while in the hospital, but in seven this was present, having been, in fact, as high as 210 systolic and 150 diastolic in one instance. In most of the patients with hypertension but negative fundi there was reason to believe that hypertension had not been present for a long time. It is true that in one of the patients who died at the age of 30 the renal disease had started twelve years previously, but we had no means of learning what the blood pressure had been during these years.

that contraction of the retinal arteries was present in all of the patients with malignant hypertensive neuroretinitis and in many of these with arteriosclerotic fundi, but here we include only those cases in which narrowing of the arterial blood columns was the sole abnormal feature. Of these patients, two had impairment of renal function, in both instances of the compensated variety with normal blood chemistry. None of the patients died while in the hospital.

Retinal Arteriosclerosis and Arteriosclerotic Retinopathy.—Retinal arteriosclerosis in the absence of changes in the retina or nerve head was observed in 70 of the patients. In 58 other patients the retinal arteriosclerosis had produced changes in the retina; in many of the cases choroidal lesions were also observed. Furthermore, in 32 of the 37 patients with malignant hypertensive neuroretinitis, retinal arterio-

TABLE 2.—*Essential Hypertension*

Ophthalmoscopic Observations	Number Cases	Deaths in Hospital	Renal Function		
			Unimpaired	Impaired	
				Compensated	Decompensated
Normal fundus	13	1	13	0	0
Contracted arteries	11	0	9	2	0
Retinal arteriosclerosis	70	9	57	11	2
Arteriosclerotic retinopathy	58	5	37	12	9
Malignant hypertensive retinitis.....	37	13	11	7	19

sclerosis was also present. Thus, 160, or 84 per cent, of our 189 patients with essential hypertension had retinal arteriosclerosis.

Prognostically, the presence of retinal arteriosclerosis or arteriosclerotic retinopathy is of significance in that it indicates that the hypertension has probably been present for a considerable time. In accord with this, it is seen from table 2 that the mortality and incidence of impairment of renal function in the patients with retinal arteriosclerosis is much higher than in those without retinal changes. On the other hand, they are much lower than in those with malignant hypertensive neuroretinitis. Moreover, as will be discussed, the rate of impairment of renal function in these patients is much slower than that in those with neuroretinitis. Patients with essential hypertension and retinal arteriosclerosis or arteriosclerotic retinopathy may get on well for many years. However, most of the patients with severe arteriosclerotic retinopathy have evidences of arteriosclerotic disease in other organs, most often the heart or the brain, and their outlook is rather poor. An exception is, however, often constituted by patients with both diabetes mellitus and essential hypertension; such patients may have marked arteriosclerotic

years. Little was known of his intervening history except that he had suffered from headaches for twelve weeks. The blood pressure was 158 systolic and 102 diastolic.

Ophthalmoscopic examination revealed both nerve heads to be clear in outline though somewhat pale (hemoglobin, 45 per cent). The arteries were markedly constricted and revealed the typical evidences of extreme arteriosclerosis described in the foregoing paragraphs. In both eyes there were recent small round hemorrhages near the disk, as well as round atrophic areas representing absorbing and absorbed hemorrhages.

The patient died a week after admission, and at necropsy chronic glomerulonephritis with marked secondary contraction was found; the process was obviously of many years' standing.

Malignant Hypertensive Neuroretinitis.—This retinal picture was found in seventeen of the patients. All of these patients gave evidence of either present or past hypertension (table 1). In most, the hypertension was marked, averaging decidedly higher than in the other groups. Fifteen of the seventeen patients had renal insufficiency with nitrogen retention. Of the remaining two, one had good renal function, while the kidneys of the other were shown to be functionally impaired by the defective outcome of the concentration test though the blood chemistry was still normal (compensated stage of impaired renal function). Eleven of the seventeen patients died while in the hospital, and several of the others were discharged in a condition in which it was evident that they would not long survive. All of the deaths were due to uremia. The long known unfavorable prognosis in this variety of retinal change is thus substantiated in the present series.

THE FUNDUS IN ESSENTIAL HYPERTENSION

In this category we have included those of our patients with arterial hypertension in whom the elevation of blood pressure was not associated with glomerulonephritis or mechanical obstruction of the urinary passages. There were 189 such cases. The ophthalmoscopic observations and certain other data are summarized in table 2.

Normal Fundus.—In thirteen of the patients with essential hypertension, ophthalmoscopic examination revealed no abnormalities. In several of these cases the hypertension was not severe and in three it was intermittent, evidently being in the initial phase of the disease. In none of these cases was renal function demonstrably impaired. Only one of the patients with normal fundi died; in this instance, cerebral hemorrhage was the cause of death, and the kidneys also revealed but slight arteriosclerosis at necropsy.

Contracted Arteries.—Marked narrowing of the arterial blood columns was observed in eleven of the patients. It should be mentioned

cases, the retinal changes had been present for many months before death. From the appearance of the necrotic lesions in the renal arterioles, however, one is led to the belief, although not the certainty, that they are of relatively recent inception. Moreover, in some of the cases the retinal lesions appeared while renal function was good and the urine exhibited only a faint trace of albumin and no blood. It scarcely seems probable that widespread necrosis of the renal arterioles with its inevitable consequences in the glomeruli should be present for any considerable time without manifesting itself in urinary changes. In several cases which later showed necrosis of the renal arterioles, we believed that we had detected the onset of arteriolar necrosis in the kidneys by the appearance of blood and larger quantities of albumin in the urine. Conceivably, then, a patient with essential hypertension and malignant hypertensive neuro-

TABLE 3.—*Age Incidence of Retinal Lesions in Essential Hypertension*

Age, Years	Normal Fundus	Narrow Arteries	Retinal Arterio- sclerosis	Arterio- sclerotic Retinopathy	Malignant Hypertensive Neuro- retinitis
0-9.....	0	0	0	0	1
10-19.....	0	0	0	0	1
20-29.....	1	0	1	0	2
30-39.....	4	1	7	7	12
40-49.....	6	7	18	15	14
50-59.....	1	2	22	26	7
60-69.....	1	1	18	9	0
70-79.....	0	0	4	1	0

retinitis may sometimes succumb before necrosis of the renal arterioles has occurred, but we have not yet observed such a case.

Malignant hypertensive neuroretinitis and the renal arteriolar necrosis it portends may appear at any stage of essential hypertension. In some of our cases, the patients had been known to suffer from essential hypertension for many years—in one instance more than twenty years—before a turn for the worse occurred and the neuroretinitis was discovered. However, in contradistinction to the arteriosclerotic retinal changes, neuroretinitis affects a decidedly higher proportion of the younger patients with essential hypertension than the older. This is shown in table 3.

The higher incidence of malignant hypertensive neuroretinitis in the younger age groups of patients with essential hypertension corresponds to the well known fact that the clinical course in such persons tends to be much more severe and rapidly fatal than in older persons with high blood pressure. The anatomic basis for this severe course lies in the fact, pointed out in the foregoing paragraphs, that those patients with essential hypertension who have neuroretinitis develop necrosis of the

retinopathy ("diabetic retinitis") with hemorrhages and areas of retinal degeneration for years while leading tolerably useful lives.

Malignant Hypertensive Neuroretinitis.—This condition was present in thirty-seven of our patients. The long known serious prognostic implication of this type of retinal lesion is immediately obvious from table 2; thirteen of the patients died of uremia while in the hospital and several more were removed in a precarious condition. In twenty-six of the patients, renal function was impaired. In nineteen of the twenty-six the impairment of renal function had reached the decompensated stage as shown by the retention of nitrogen in the blood. In accordance with the observations of Keith and his co-workers, malignant hypertensive neuroretinitis may appear in a patient with essential hypertension while renal function is not demonstrably impaired, and this adequate functional state of the kidney may persist for a considerable time, exceptionally even for years. However, more often such patients soon show evidence of functional impairment of the kidneys. The progress of the impairment of renal function in the presence of malignant hypertensive neuroretinitis is generally much more rapid than in patients with only arteriosclerotic changes in the fundus.

The reason for the rapid progress of impairment of renal function in most cases of essential hypertension with malignant hypertensive neuroretinitis seems clear from the anatomic observations in those of our cases that came to necropsy. In all ten of the necropsies in cases in which the patients had had essential hypertension and malignant hypertensive neuroretinitis, necrosis of the arterioles in the kidney was found.²⁹ In all instances the anatomic picture of the kidneys was that described by Fahr³⁰ as "malignant sclerosis," namely, necrosis, endarteritis and thrombosis of the renal arterioles, necroses and proliferative changes in the glomeruli, in addition to the arteriolosclerosis and glomerular hyalinization which are also found in the usual ("benign") case of essential hypertension. On the other hand, necrosis of the renal arterioles was not present in any of the eleven cases of essential hypertension without malignant hypertensive neuroretinitis in which the patients came to necropsy.

As far as our material is concerned, then, the presence of malignant hypertensive neuroretinitis in essential hypertension is diagnostic of the occurrence of necrosis of the renal arterioles. We suspect, however, that the retinal changes may precede the actual appearance of arteriolar necrosis in the kidneys, for the following reasons: In several of the

29. The anatomic studies were made by Dr. Paul Klemperer.

30. Fahr, in Henke and Lubarsch: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1925, vol. 6, p. 405.

ment with ultraviolet rays. In the region of the hip was a draining sinus. The heart was slightly enlarged to the left. The liver and spleen were not demonstrably enlarged. The blood pressure was as high as 196 systolic and 116 diastolic. The urine contained a small quantity of albumin and a few casts. Study of renal function revealed it to be severely impaired; in a concentration test the specific gravity did not rise above 1.012, and the blood contained 70 mg. of urea nitrogen per hundred cubic centimeters. The Bennhold test with congo red showed that only 22 per cent of the dye remained in the blood stream at the end of an hour, instead of the normal of over 70 per cent; in the absence of great albuminuria, such a result is highly suggestive of the presence of amyloidosis.

Ophthalmoscopic examination revealed the presence of arteriosclerotic retinopathy. The retinal arteries showed a moderate degree of arteriosclerosis. The disks appeared normal. Above, below and to the temporal side of the right disk were linear hemorrhages, in close relation to the vessels. About half way between the left disk and the macular region was a white area of degeneration, roughly triangular and sharply delimited. There were several minute white areas above the macula. In the right retina were two small hemorrhages.

The condition of the patient rapidly became worse, and retention of urinary constituents in the blood became more severe (urea nitrogen, 224 mg. per hundred cubic centimeters). He died of uremia on December 19.

At necropsy amyloid contracted kidneys obviously of long standing were found.

SUMMARY

1. In 274 cases of hypertensive and renal diseases the ophthalmoscopic observations have been studied in relation to the clinical picture; in 39 of the cases, postmortem observations were also made.

2. The concept of albuminuric retinitis includes three distinct pathogenetic entities, which can most often be differentiated with the ophthalmoscope: (a) arteriosclerotic retinopathy, (b) malignant hypertensive neuroretinitis and (c) choked disk due to increased intracranial tension from edema of the brain.

3. The ophthalmoscopic characteristics of these three types of retinal changes are described, and their occurrence and prognostic significance in the individual types of hypertensive disease investigated.

4. In all of the ten cases of essential hypertension with malignant hypertensive neuroretinitis in which the patients came to necropsy, necrosis of the renal arterioles was present. On the other hand, necrosis of the renal arterioles was absent in eleven instances of essential hypertension without malignant hypertensive neuroretinitis that were studied at necropsy.

5. Instances are described of malignant hypertensive neuroretinitis in a patient with arterial hypertension due to suprarenal tumor and of arteriosclerotic retinopathy accompanying hypertension resulting from amyloid contracted kidney.

renal arterioles. The necrosis of the renal arterioles with its attendant changes in the renal parenchyma results in severe and generally rapidly progressive renal insufficiency.

Parenthetically it may be remarked that while the presence of malignant hypertensive neuroretinitis in a patient with essential hypertension indicates that necrosis of the renal arterioles is either present or will appear, it does not have this significance in glomerulonephritis. In fact, we had not observed arteriolar necrosis in chronic glomerulonephritis—although it does occur in the acute and subacute stages of the disease—until Dr. Paul Klemperer recently showed us this change in such a case. Even in this instance, only isolated arterioles were affected.

THE FUNDUS IN AMYLOID KIDNEY

In the vast majority of instances of amyloid disease of the kidneys, there are no retinal changes. The reason is, of course, that arterial hypertension is rare in amyloid kidney. However, there are cases of renal amyloidosis with hypertension, and in extremely rare instances this results in retinal lesions. Dickinson³¹ mentioned such a case, and Litten³² observed two instances of typical "Bright'sche Retinitis" in several hundred cases of amyloid disease. In their recent paper on amyloid contracted kidney, Noble and Major³³ mentioned in a table that albuminuric retinitis was present in one case. In our series, there was a case of amyloid contracted kidney with arteriosclerotic retinopathy. As such cases are apparently great rarities, the principal features will be summarized briefly.

CASE 3.—M. C., a man, aged 37, was admitted to Mount Sinai Hospital on Nov. 14, 1929, complaining of pain in the left side of the chest and left shoulder and vomiting.

Since the age of 5 years he had suffered from tuberculosis of the left hip, a sinus persisting despite three operations. He had had nocturia (up to six times a night) as far back as he could remember. For three years previous to admission to the hospital he had suffered from headaches; sometimes these were accompanied by nausea and vomiting, which had become much more frequent. About six weeks before admission he began to suffer from pain in the left shoulder and precordial region which radiated down the left arm to the finger tips. At first this pain appeared only after walking or other exercise, but shortly before admission it also manifested itself when he was at rest, especially at night.

At the time of admission to the hospital the patient was emaciated. There was a diffuse brownish pigmentation of the skin, probably largely the result of treat-

31. Dickinson: *Treatise on Albuminuria*, ed. 2, New York, William Wood & Company, 1881, p. 190.

32. Litten, in Zuelzer and Oberlaender: *Klinische Handbuch der Harn- und Geschlechtsorgane*, Leipzig, F. C. W. Vogel, 1894, vol. 2, p. 131.

33. Noble, J. F., and Major, S. G.: *Renal Insufficiency in Amyloid Disease*, *Arch. Path.* 8:762 (Nov.) 1929.

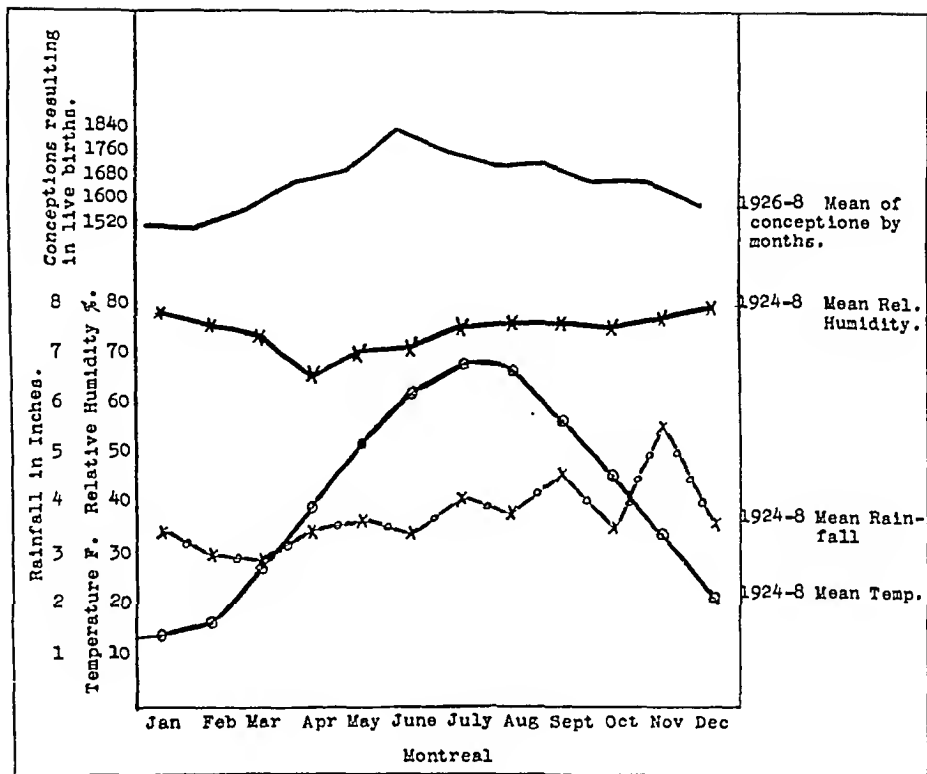


Chart 1.—Seasonal variations in the conception rate in Montreal.

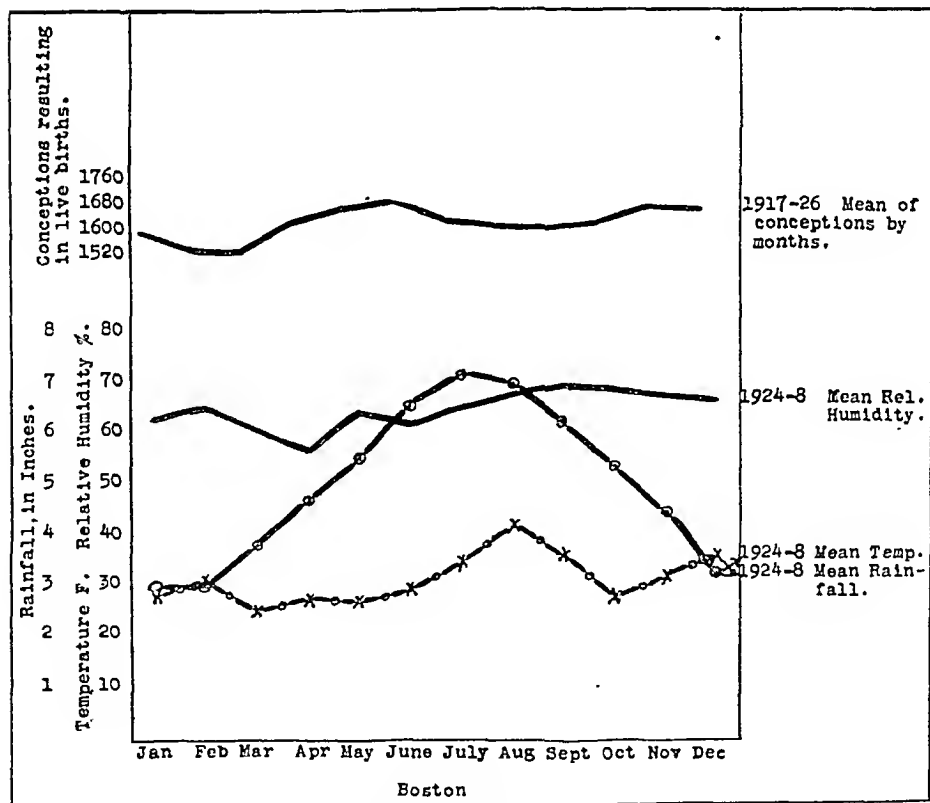


Chart 2.—Seasonal variations in the conception rate in Boston.

DOES CLIMATE AFFECT THE HUMAN CONCEPTION RATE?*

C. A. MILLS, M.D.
AND
MRS. F. A. SENIOR
CINCINNATI

In an effort to ascertain the extent of climatic effects on the human organism in health and disease, we have studied its effect on such metabolic diseases as diabetes mellitus, pernicious anemia, exophthalmic goiter and Addison's disease. In these diseases there was found a distinctly lowered death rate in the warmer regions that show, in general, a depression of the metabolic rate by the heat. The people of these regions possess relatively low blood pressures, and have distinctly less angina pectoris than is found in the cooler countries.

Since the climatic effects mentioned are probably exerted mainly through the endocrine glands (pancreas, thyroid, suprarenals), it was deemed advisable to determine whether a similar depression was exercised on the sex glands. For this purpose the birth statistics of different cities, states and countries were obtained. The numbers of births in each month for a number of years were taken, the mean for each month obtained, and the twelve months equalized to a thirty-one day basis for comparison. Due attention was paid to February irregularities in this calculation. Also, where the population of the unit studied changed more than 1 per cent a year during the period covered by the statistics used, due correction was made for the effect of this increase or decrease on the monthly birth rate during the mean year. The corrected monthly births were then transposed to conception times by counting back nine months and ten days, and these "conceptions resulting in live births" were plotted as shown in the graphs. It is, of course, obvious that any climatic effect should be expected to be correlated directly with conception time rather than with the time of birth, since births are only more or less inevitable consequences of the conceptions.

For a number of localities the mean temperature, relative humidity and rainfall by months are also charted to show their relationship to the monthly conception curve. All graphs are drawn with the bottom of the chart as the zero line.

Beginning with the more northern cities and countries, we see the conception rate in Montreal to be rather depressed in the late winter,

* Submitted for publication, May 21, 1930.

* From the Department of Internal Medicine, University of Cincinnati.

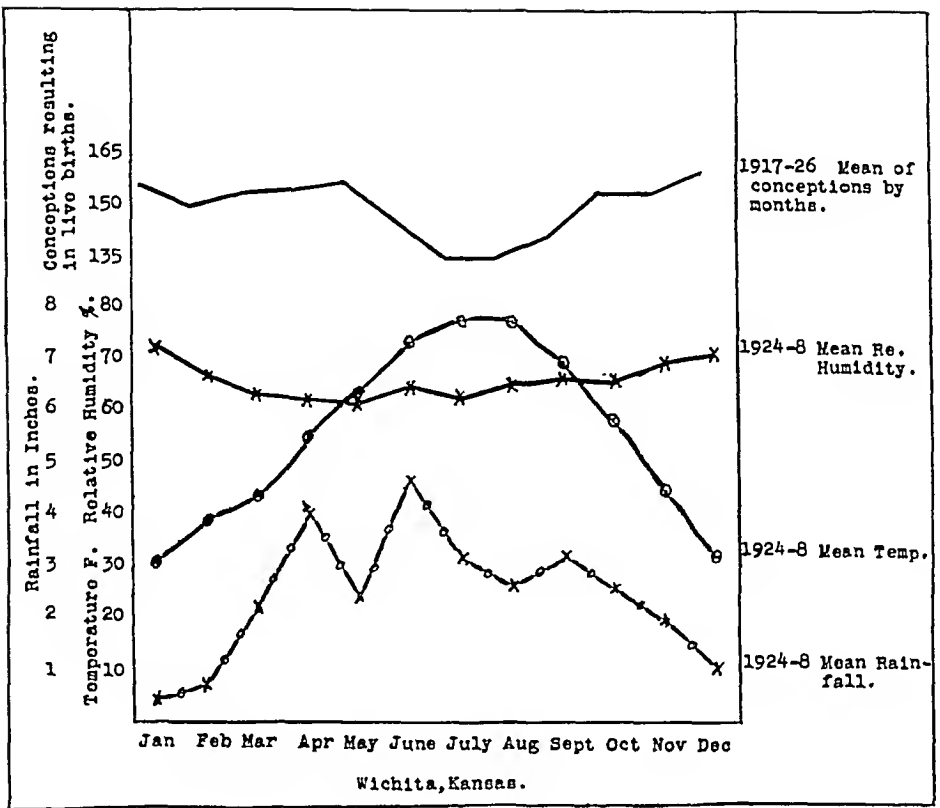


Chart 4.—Seasonal variations in the conception rate in Wichita, Kan.

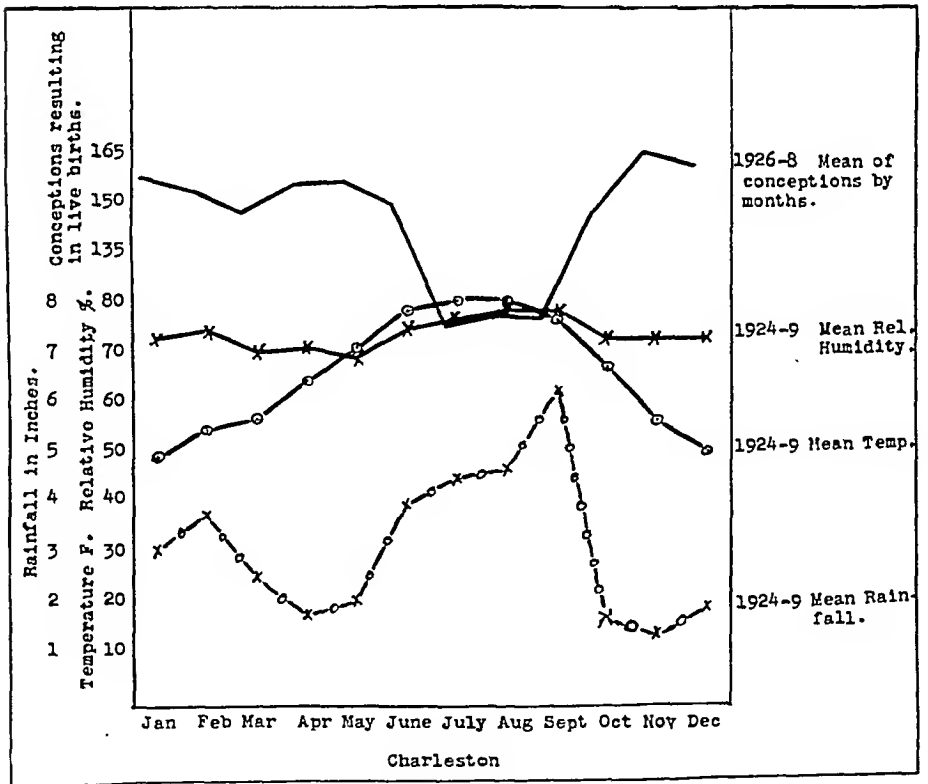


Chart 5.—Seasonal variations in the conception rate in Charleston.

to rise steadily to a June peak, and then to decline gradually again to late winter. The rise in the mean monthly temperature to about 68 F. for July and August seems to be without depressive effect on conceptions.

A little farther south, however, where the mean monthly temperature for July and August rises above 70 F., there is a depressive influence on conceptions. Boston, with a July and August mean of 71 F., shows a 6 per cent reduction in conception rate. Chicago exhibits a marked late winter depression and a mild summer heat effect.

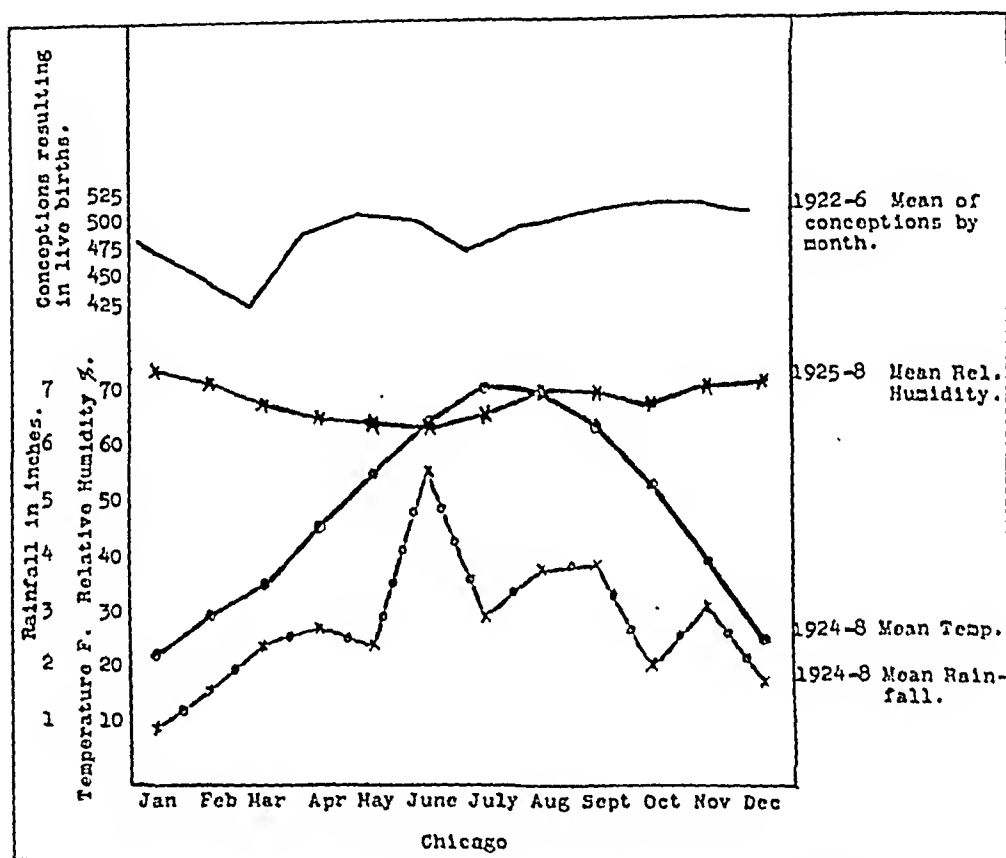


Chart 3.—Seasonal variations in the conception rate in Chicago.

Wichita, Kan., in which the mean July and August temperature rises to 78 F., suffers a 14 per cent reduction in the conception rate. The mean temperatures of 82 F. in Charleston, S. C., and 83 F. in Tampa, Fla., are accompanied by corresponding depressions of 27 and 31 per cent in the conception rate.

On the other hand, in the cities of the Pacific Coast, where the mean temperature is more stable, in no case rising above 70 F. for the summer months, there is no summer depression of conceptions. Even as far south as San Diego and Los Angeles, there is no significant summer effect.

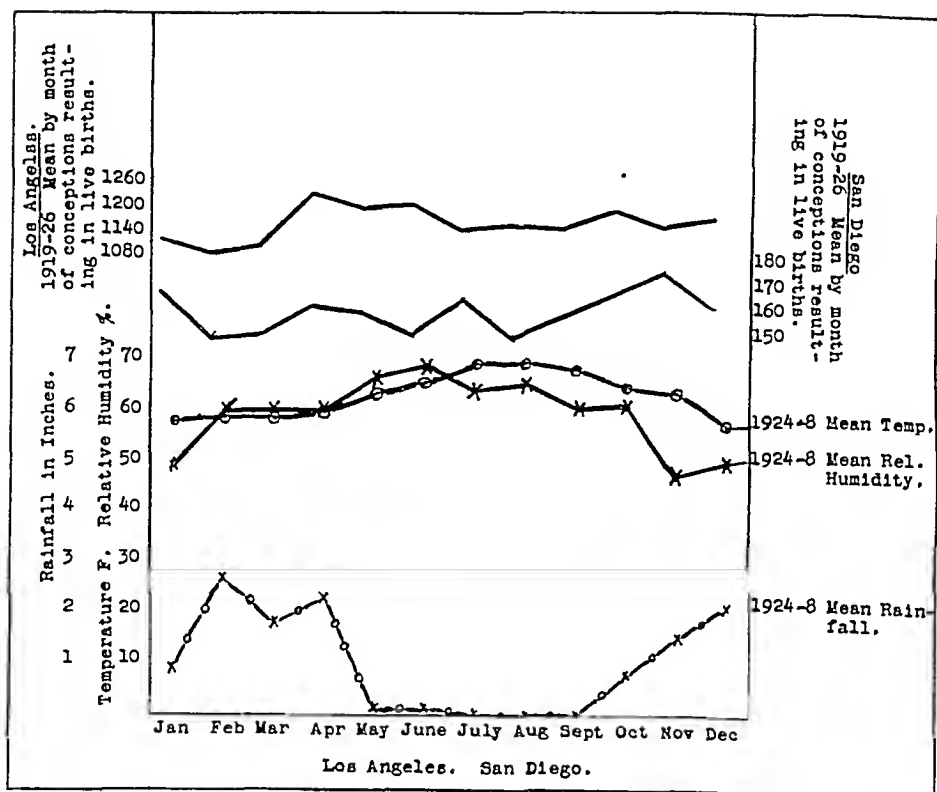


Chart 7.—Seasonal variations in the conception rate in Los Angeles and San Diego.

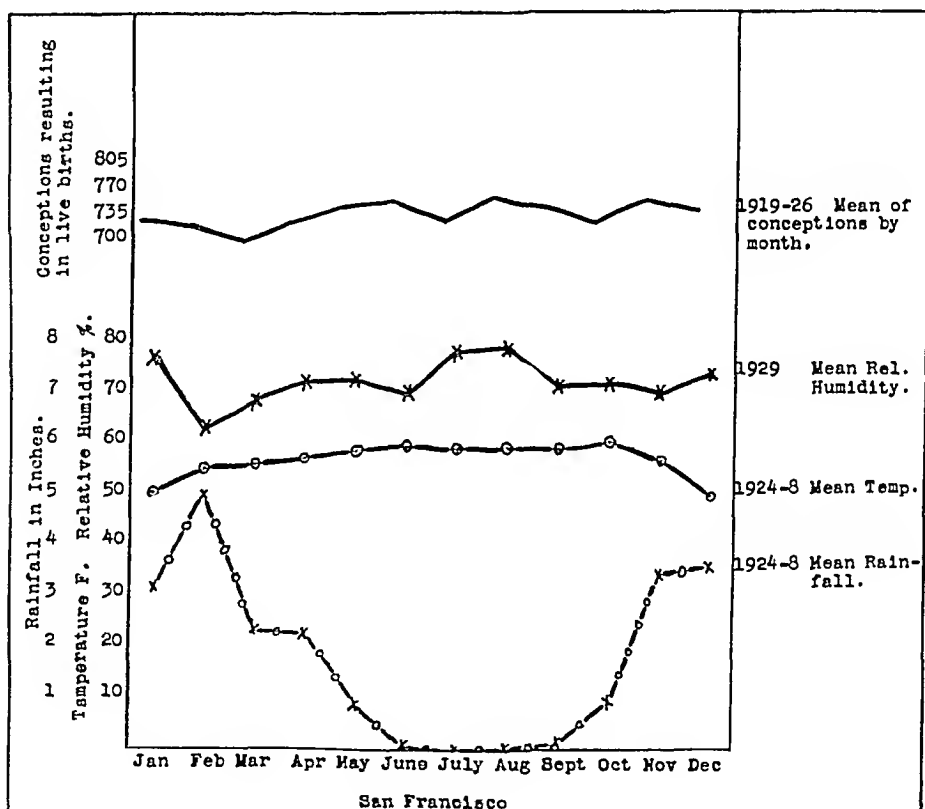


Chart 8.—Seasonal variations in the conception rate in San Francisco.

A similar study of states in various latitudes from Maine to Florida gives results similar to that from the cities. In the north the spring depression is most marked, with the rate highest in the summer; in the central states the heat depression of July and August is evident, and farther south this becomes more and more marked.

In order to show that the variations in conception rate are not necessarily correlated with the marriage rate, graphs are shown for Belgium and Switzerland. Here it is seen that although the June peak in con-

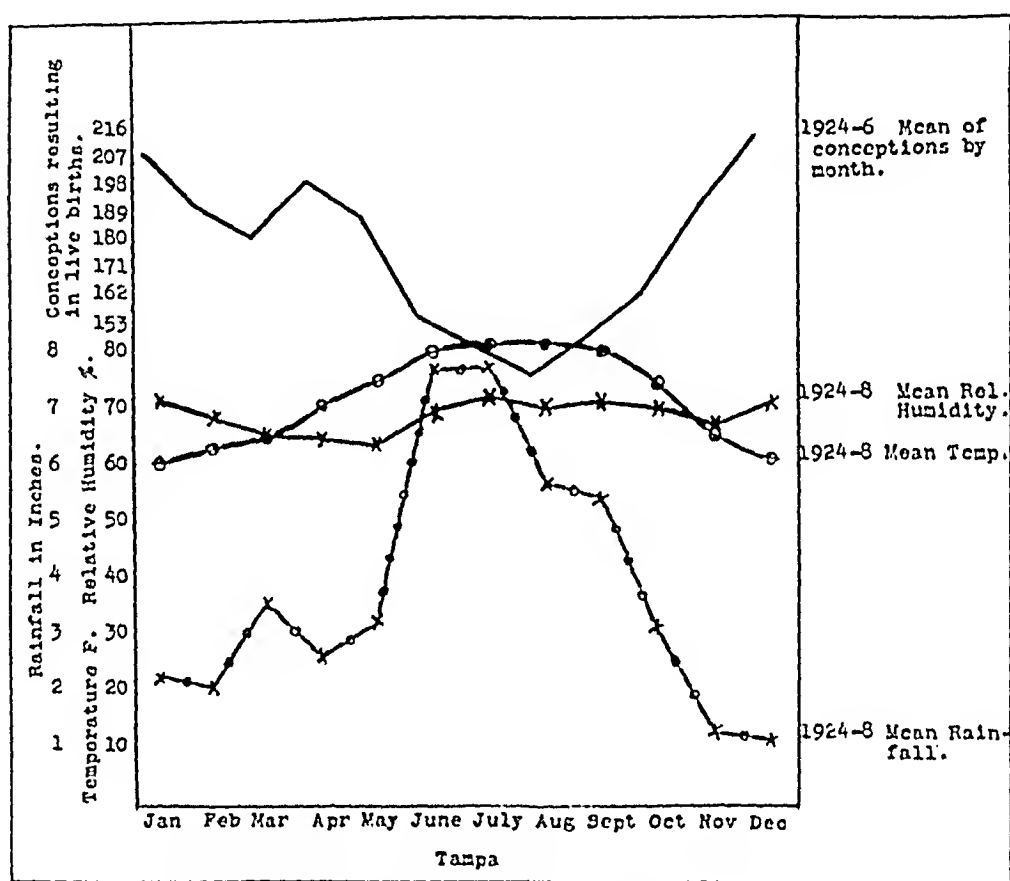


Chart 6.—Seasonal variations in the conception rate in Tampa, Fla.

ceptions coincides well with a similar marriage peak, the fall marriage peak does not produce a noticeable effect on conceptions.

In Japan the climatic effects are most striking. The spring months of April, May and early June are almost perfect so far as temperature is concerned, but from the middle of June to early September the humidity is almost constantly high, day and night, while the mean temperature rises to 99 F. The mean monthly temperature and rainfall recorded on the graph represent the means obtained for 1928 from nine observation stations scattered throughout Japan. The graph shows the striking changes produced in the conception rate by these climatic changes. There is a 50 per cent fall in conceptions during their tropical

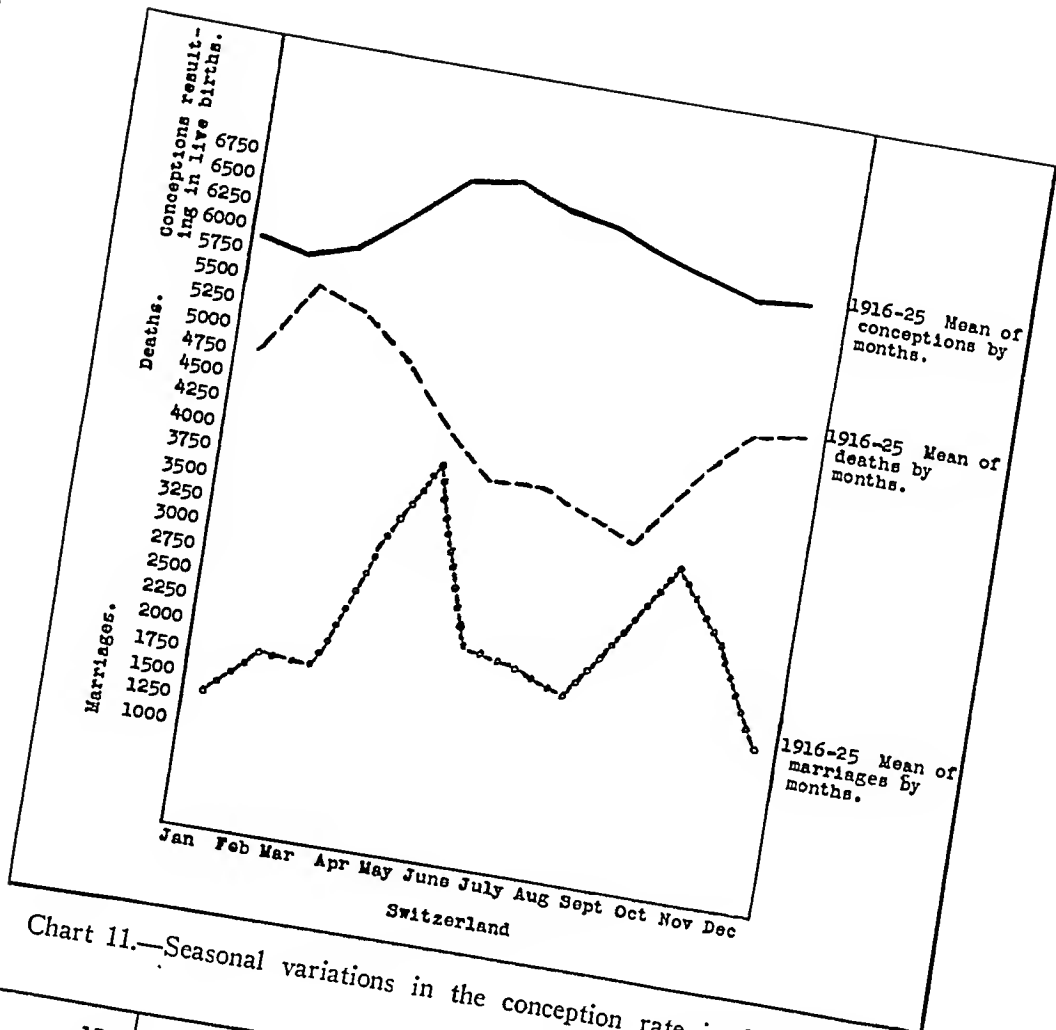


Chart 11.—Seasonal variations in the conception rate in Switzerland.

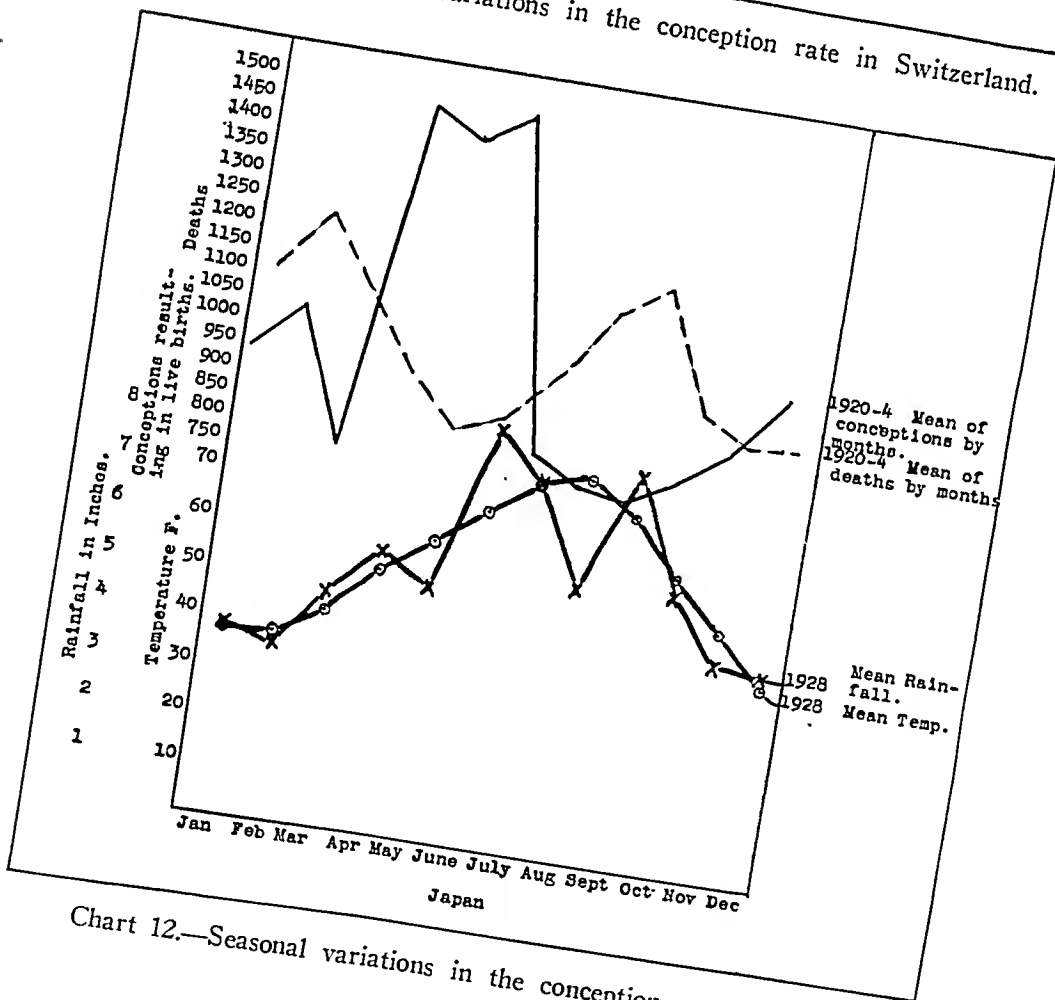


Chart 12.—Seasonal variations in the conception rate in Japan.

summer period! Calculation has shown that not over 10 per cent of the spring rise in conceptions here could be attributed to the increase in the marriage rate.

No doubt many persons reading this article will be inclined to attribute the depressions in conception rate during the hot months to a diminution in the frequency of intercourse during the hot weather, but such

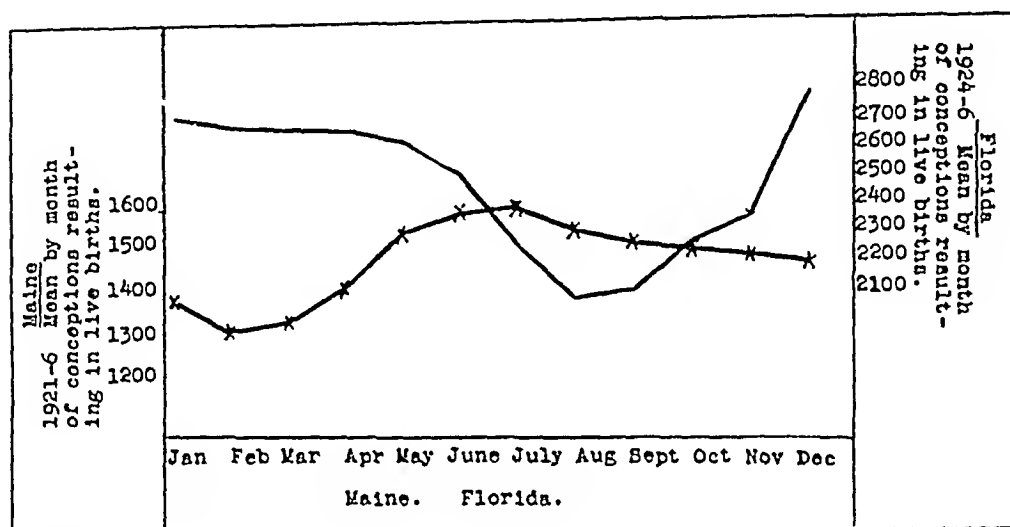


Chart 9.—Seasonal variations in the conception rate in Maine and Florida.

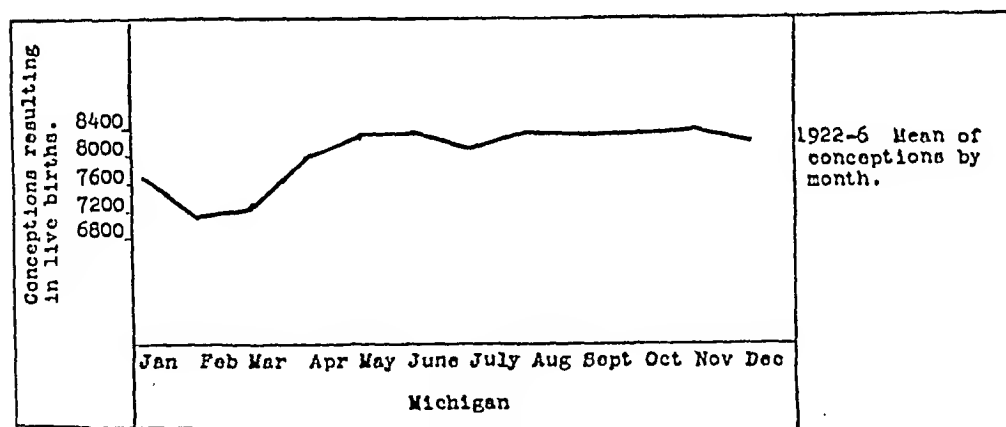


Chart 10.—Seasonal variations in the conception rate in Michigan.

is not the case. Dr. T. J. LeBlanc (personal communication) obtained statistics on the frequency of use of houses of prostitution by the male population of Japan, and these statistics show no significant depression of male sexual activity during the hot summer months. We may, then, conclude that male sexual activity is not much influenced by heat, and in a country like Japan it is mainly the male that dominates this question. Since Japan shows the most marked seasonal variations in conceptions, the inference is that a biologic reduction in fertility is produced by the heat.

VITAL CAPACITY IN COLLEGE WOMEN _ .

I. STANDARDS FOR NORMAL VITAL CAPACITY IN COLLEGE WOMEN *

ABBY H. TURNER, PH.D.

SOUTH HADLEY, MASS.

A former paper¹ on vital capacity in college women included standards derived from the physical examinations of 1,150 Wellesley freshmen. The apparatus was as good as was available when the data were gathered, 1922 to 1924, and it was used with systematic regard for accuracy. To verify or revise these standards, the vital capacities of the freshmen at Mount Holyoke College were carefully taken during the years 1925 to 1929 by the department of physical education, with an excellent Collins spirometer. The group, after the omission of oriental students and those with crippled thorax, numbered 1,337, and was, as far as is known, a typical group of freshmen—healthy young women aged about 18. The age range was small, from 16 to 23, with the very great majority from 17 to 19 years of age.

Since it became apparent from the observation of many students that those who were most likely to give inaccurate results in the regular fall physical examination were the students with low vital capacity, all students in this group were reexamined, and about one-third raised their records appreciably. They either had not understood how to use the spirometer the first time, simple as the test is, or embarrassment prevented their showing what they really could do. Their second figures were approximately like those that they repeat throughout their course. This merely indicates the need of careful and repeated studies of students in working with any functional test, if the results are to be valid. Speed in giving the tests cannot be paramount, as it too often is in the rapid routine of the freshman examination.

The statistical treatment of the figures was made by the usual methods. Our results were verified by the department of statistics of the Harvard School of Public Health, and regression equations were derived by them for the prediction of vital capacity from height, weight and surface area. They also prepared the charts for easier comparison of individual cases with normal results.

The results of this study are given in the table. Figures from the Wellesley group and also those from the Stanford study of Pasmore

* Submitted for publication, June 25, 1930.

* From the Department of Physiology, Mount Holyoke College.

1. Turner, A. H.: The Vital Capacity of College Women, *Am. Phys. Ed. Rev.* **32**:593, 1927.

It cannot be demonstrated at present whether only one sex or both are involved in the depression. It is known that raising the temperature of the testicles by 2 or 3 C. (35.6 or 37.4 F.) will inhibit spermatogenesis. Some stock breeders claim that a ram loses his effectiveness in the summer if his scrotum is enclosed in heavy flannel to retain body heat.

While there seems to be no doubt, from the graphs presented, that there is a seasonal depression in conceptions when the mean monthly temperature rises above 70 F., it must not be inferred that the annual birth rate in the tropics is lower than that in the temperate regions. Indeed, just the opposite is the case; but too many factors enter into determining the total birth rate for us to derive any value in discussing it here. Different populations should not be compared in this respect; but we may well compare seasonal changes occurring in given populations.

In 1925, Reed¹ presented graphs of the monthly birth rate in the United States and Great Britain. From the graphs presented in the present article it is seen that there is really no single seasonal birth curve in this country, the north and south being almost the reverse of each other. It is of special note to observe that the peak of conception rate in the various graphs presented most often occurs when the mean monthly temperature is around 65 F. It was at about this same temperature that Huntington² found human efficiency along various lines of endeavor to be highest.

In conclusion, we may state that human fertility, as indicated by the conception rate, is highest in any given population at a temperature of about 65 F., and that it is reduced during the low temperatures of the northern winter and by mean summer temperatures above 70 F. The summer depression is roughly proportional to the rise in the mean temperature above 70 F. These changes in conception rate are not dependent on changes in the marriage rate or sexual activity of the population, and must therefore represent actual variations in human fertility.

1. Reed, Lowell J.: *Am. J. Pub. Health* **15**:948, 1925.

2. Huntington, Ellsworth: *World Power and Evolution*, New Haven, Conn., Yale University Press, 1920.

Points shown in the table to which attention is called are as follows: The vital capacity of the Mount Holyoke group is distinctly higher than that of the Wellesley group. Each year as the data were collected my associates and I saw this higher result, and in looking for a reason we seemed to find it in the ease with which the Collins spirometer is blown. In this instrument there is no constriction of the tube between mouth and bell, all moving parts are light, the bell is well counterpoised, and there is no excess pressure in the bell at the end. We think, therefore, that these results represent a real advance in accuracy, and not that the girls at Mount Holyoke are of higher vital capacity than are the Wellesley girls of approximately the same size. If vital capacities are to mean anything in the study of human welfare, they must be taken with care to secure the subject's real maximum. The improvement also in the correlation of these measurements with other bodily measurements may indicate that these figures are better ones. It is of interest to note that the average vital capacity in liters divided by the average surface area gives 2.07, practically West's figure of 2 liters per square meter of body surface as the normal for women,⁶ and when the vital capacity in cubic centimeters is divided by the average height in centimeters one obtains 20.1, again almost the same as West's formula for women of 20 cc. for each centimeter of standing height.

The regression equations, which were determined for the several correlations, are given here. This is a more accurate mode of prediction than the simple device just mentioned. By them, the average vital capacity for any height, weight or surface area can be calculated easily. For instance, let x equal the measured height; then y , the average vital capacity, can be obtained by substituting for x the observed height in the equation. Surface area is derived from height and weight according to the method of DuBois,⁷ for which nomogram and tables are readily found.

Height	$y = 0.0368x - 2.706$
Weight	$y = 2.017 + 0.023x$
Surface area	$y = 0.279 + 1.901x$

By looking at the coefficients of correlation, it will be noted that the equations for height and surface area give much better modes of prediction than that for weight.

From charts 1, 2 and 3, the average vital capacity for any observed height or weight or calculated surface area can be quickly determined.

6. West, H. F.: Clinical Studies on the Respiration, *Arch. Int. Med.* **25**:306 (March) 1920.

7. DuBois, D., and DuBois, E. F.: Clinical Colorimetry, *Arch. Int. Med.* **17**:863 (June) 1916.

and Weymouth² are given for comparison with the recent figures from the Mount Holyoke group. The data in the Minnesota study by Boynton³ are unfortunately not in a form for ready comparison, nor are the tables for women compiled by Myers,⁴ but a footnote to the table indicates the general nature of these results. The methods used in obtaining data at McGill University (Herriott⁵) are not fully enough

*Determinations on Five Freshmen Classes at Mount Holyoke College, 1925 to 1929
Inclusive, Totaling 1,337 Students**

	Mount Holyoke	Wellesley	Stanford
Number tested.....	1,337	1,150	430
Averages:			
Height, cm.	162.83	162.9	161.5
Weight, Kg.	55.50	54.97	54.9
Surface area, sq.m.	1.58	1.585	1.571
Vital capacity,† liters.....	3.28	2.99	2.769
Standard deviations:			
Height.....	5.9965	5.685	5.37
Weight.....	7.1950	8.465	7.73
Surface area.....	0.1123	0.103	0.112
Vital capacity.....	0.4384	0.478	0.466
Coefficients of variation:			
Height.....	0.0369	0.0348	0.033
Weight.....	0.1297	0.151	0.122
Surface area.....	0.0711	0.065	0.071
Vital capacity.....	0.1329	0.159	0.169
Coefficients of correlation:			
Height : weight.....	0.4410	0.591
Vital capacity : height.....	0.4958	0.354†	0.338
Vital capacity : weight.....	0.3754	0.2445‡	0.358
Vital capacity : surface area.....	0.4870	0.292§	0.400

* For comparison, figures from Wellesley and Stanford groups are also given. As compared with the tables of Myers, 1925, the figures from the Mount Holyoke group give about 107 per cent. Our averages were applied to his tables for calculating vital capacity from height and weight.

† Height and logarithm vital capacity were used here.

‡ Logarithm vital capacity and logarithm weight were used here.

§ Logarithm vital capacity and logarithm surface area were used here.

described to enable one to judge whether the spirometer used was comparable with that used at Mount Holyoke, but the figures are so far below those we obtained that they are not referred to in detail.

2. Pasmore, E. E., and Weymouth, F. W.: The Relation of Vital Capacity to Other Physical Measurements in Women, *Am. Phys. Educ. Rev.* **29**:166, 1924.

3. Boynton, R. E.: A Comparison of Normal Standards for the Vital Capacity of the Lungs of Women, *Arch. Int. Med.* **33**:292 (March) 1924.

4. Myers, J. A.: The Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925.

5. Herriott, J. S.: Research Quart. *Am. Phys. Educ. A.* **1**:46, 1930.

Find the observed or calculated measurement at the bottom of the chart. Follow the proper line vertically until it intersects the oblique line 0; then proceed from this intersection to the left margin where the average vital capacity for the measurement in question will be found in liters. With this the subject's actual vital capacity can be readily compared.

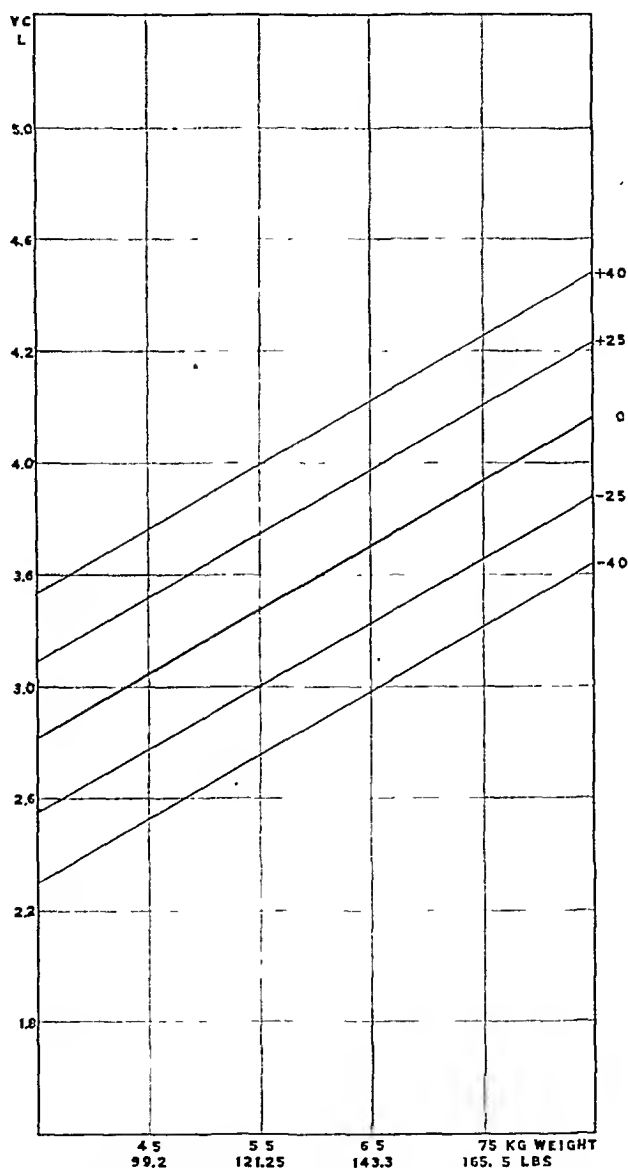


Chart 2.—The average vital capacity for young adult women of any weight and the position of 50 and 80 per cent of the groups of different weights.

Vital capacity varies much among persons of a single height, weight or surface area. It is desirable, therefore, not only to know that a particular subject is, say, 10 per cent low in vital capacity, but to know how many other persons of that height show the same figure. On the charts, the lines +25 and -25 include between them 50 per cent of

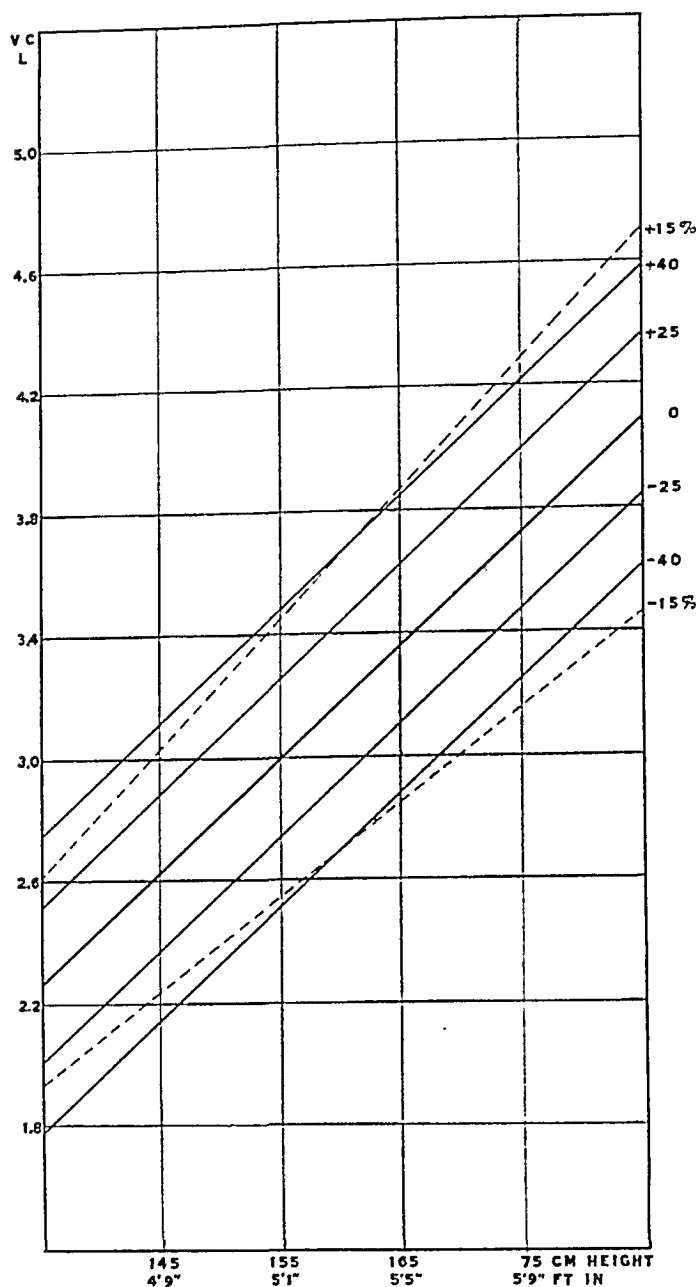


Chart 1.—The average vital capacity for young adult women of any height and the position of 50 and 80 per cent of the groups of different heights. In this and the following charts, *v.c.* indicates vital capacity; the 0 line, the line of average vital capacity for the heights given at the bottom of the chart; the +25 and -25 lines, the limits of 50 per cent of the vital capacities; the +40 and -40 lines, the limits of 80 per cent of the vital capacities. Above line +15 per cent and below line -15 per cent lie the vital capacities that are removed by more than 15 per cent from the average value. To find average vital capacity: from height of subject at bottom of chart proceed vertically to line "0"; at the left margin opposite this intersection will be found the average vital capacity for the height in question.

165.6 cm.; vital capacity, 3.396 liters. By reference to our height chart, it is seen that for the height 165.6 cm. the average vital capacity is 3.39, as close an agreement as could be asked. The distribution is as follows:

	Theoretical number	Observed
Above + 40	28-29	34
Between + 40 and + 25.....	42-43	35
Between + 25 and 0.....	71-72	65
Between 0 and - 25.....	71-72	75
Between - 25 and - 40.....	42-43	54
Below - 40	28-29	22

This agreement is approximately like that obtained from successive classes at Mount Holyoke. The high average height, vital capacity and high number above the + 40 line in the Vassar study seem due to a considerable group of tall students with high vital capacity rather than to a general shift in the average, as is shown by the fact that of the total number more than half are below the 0 line. This skewness of distribution toward the high end of the vital capacity curve we also found at Mount Holyoke in nearly, though not quite, all classes studied. It may be related to the unequal participation of the students in sports, but this phase of the subject will be considered in the next paper.

In considering whether vital capacity is being measured as accurately as possible, McCloy⁸ raised the question of the importance of temperature. Careful consideration has been given to the possibility of correcting to body temperature, as he suggests, the volume of air collected. There are serious difficulties in the way of making such a correction. Although the air in the machine cools rapidly to about the temperature of the room, if the machine is left filled, since the walls of the bell are thin and the metal so placed as to conduct heat easily to the water jacket, an accurate determination of the temperature of the expired air is not easy to obtain, because it probably changes at different rates in different cases, since some girls breathe out rapidly, some slowly. For the quantities of air concerned in our series, the variations on different days at the ordinary range of room temperatures, say 10 C. as a maximum, cannot be more than from 100 to 150 cc., a quantity within the range of variation in successive determinations made with all possible care by persons used to the machine. This room temperature quantity seems to fit the needs of the medical profession—to whom, after all, this measurement is of the greatest consequence—since simplicity of performance is much to be desired in any test. The differences, further, between the average vital capacity and any vital capacity that becomes important from the standpoint of disease or of physical fitness

8. McCloy, C. H.: *Am. Phys. Educ. Rev.* **32**:323, 1927.

the whole number of persons measured; the lines $+40$ and -40 similarly include 80 per cent of the total number. We should expect to find, then, about 10 per cent of any large group above the $+40$ line and as many below the -40 line.

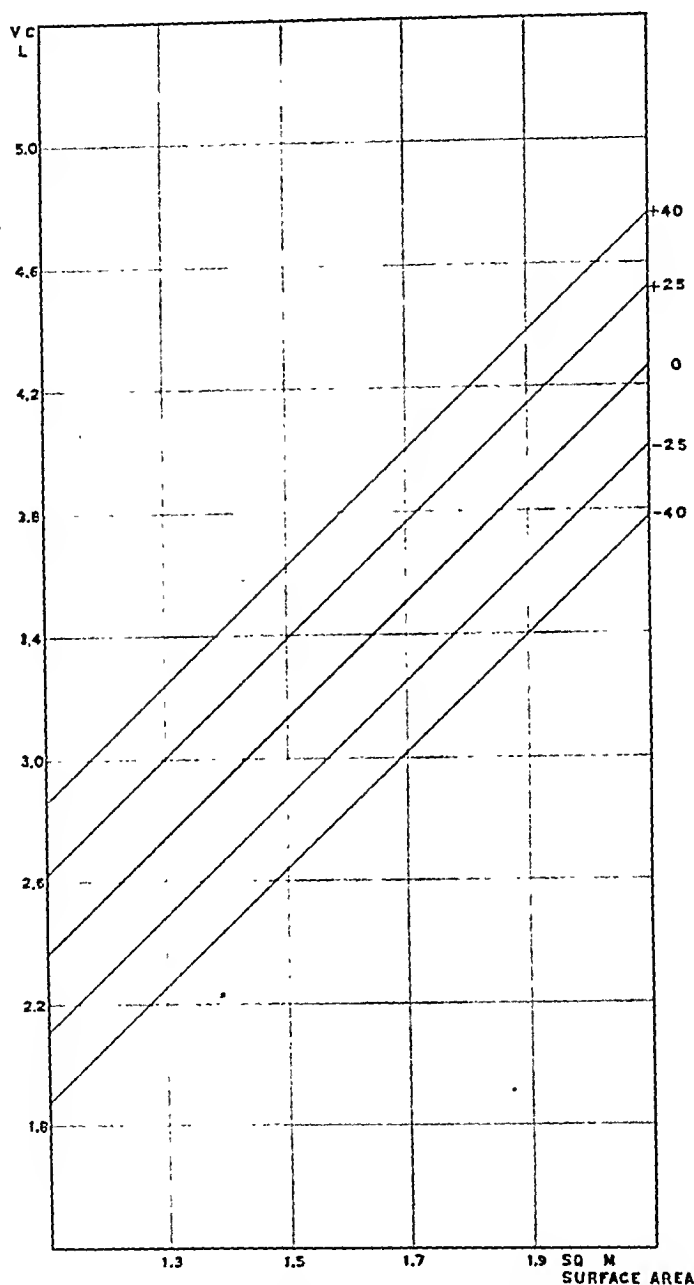


Chart 3.—The average vital capacity for young adult women of any surface area and the position of 50 and 80 per cent of the groups of different surface areas. Surface area is derived from height and weight according to the DuBois method.

It has been possible to try out the usefulness of these determinations on one class at Vassar College through the cooperation of Dr. Charlotte Haywood of the Physiology Department who charted last fall's freshman class of 285 students. The averages for this class are height,

VITAL CAPACITY IN COLLEGE WOMEN

II. A STUDY OF STUDENTS WITH HIGH AND LOW VITAL CAPACITY *

ABBY H. TURNER, PH.D.

SOUTH HADLEY, MASS.

Dreyer, the Englishman who has done so much work in vital capacity studies, is quoted by Myers¹ as follows: "If a person is found to have as much as 10 per cent less vital capacity than is normal for his class, it is *probable* that he is suffering from some health depressing condition, and if he is as much as 15 per cent below the normal limit, it is *practically certain* that he is abnormal in this respect." The work of Myers and others narrows the range of diseases expected to those of the lungs, heart and thorax.

It therefore seemed desirable to study carefully the students with low vital capacity in the group of 1,337 students used for the establishment of the new standards given in the first paper of this series (Turner²). All students more than 15 per cent under the average for their height (see chart 1, this issue, p. 933) have been kept under observation for a period varying from four academic years (two classes) to one academic year (the class entering college in the fall of 1929). This study was made with the cooperation of the medical department and the department of physical education. The program followed was that of interviews in the fall and spring with each student, at which times her vital capacity was checked and her athletic and health history talked over. A preliminary report on this study was made in 1927 (Turner³).

The following points were taken up, with the student, the college physicians, the gymnasium staff, or with all of them as became necessary:

1. Precollege history of activity as shown by participation in sports in and out of school, by summer programs, going to camps, and so on.

2. Special activities, such as prolonged study of vocal music or practice on wind instruments, etc.

3. Previous history of disease, especially those diseases affecting vital capacity (diseases of heart, lungs and thorax). One leading question that often brought evidence otherwise not recorded, in spite of medical histories given by parents

* Submitted for publication, June 25, 1930.

* From the Department of Physiology, Mount Holyoke College.

1. Myers, J. A.: *The Vital Capacity of the Lungs*, Baltimore, Williams & Wilkins Company, 1925.

2. Turner, A. H.: *Vital Capacity in College Women*. I. Standards for Normal Vital Capacity in College Women, this issue, p. 930.

3. Turner, A. H.: *The Vital Capacity of College Women*, Am. Phys. Ed. Rev. **32**:593, 1927.

will be of a much greater magnitude than the corrections involved for temperature. Hence, for reasons of general convenience and because the quantities involved are not greater than chance variations, it has seemed best not to attempt to introduce the temperature correction, tempting as it is from the standpoint of ideal accuracy.

SUMMARY

The study of the vital capacities of 1,337 freshman women at Mount Holyoke College has resulted in the presentation of a set of statistical data, regression equations and charts relating vital capacity to height, weight and surface area. The correlation with standing height is the best and with surface area only slightly less good. As previously determined, the weight correlation is distinctly less close.

have had many vocal lessons; three have done significant work on farm or ranch; one is an Olympic swimmer. Two have lived in the country, where they "yelled" to see how far they could make their friends hear across country, a real sport for them. None of these factors are found in the group with low vital capacity.

3. *Previous History of Disease.*—In the group with low vital capacity there are each year a few students, perhaps three or four, with lasting cardiac defects either congenital or, more often, a sequel to some infection. These students are expected to have low vital capacity, but it is always surprising to find by no means all of the students with cardiac disorders in this group, for they are found in almost equal numbers in the normal group and even in the group with high vital capacity. Since it is difficult to find out the exact diagnosis in these cases, which obviously can be of little limitation or the students would not be in college, they have not been omitted from the group as a whole.

Myers¹ gives the average vital capacity for students who have had pneumonia as below the general average, but in the group of students with high vital capacity at Mount Holyoke there were proportionally almost as many persons who had had pneumonia as among the students with low vital capacity, and in the family history is noted seemingly equally severe disease. It seems, therefore, that in many cases the recovery is complete, and that one can have no assurance that an observed low vital capacity is due to pneumonia, though this may often be the case.

We have found no cases in which recovery from pulmonary tuberculosis has been known. There are several students in college with deformed thorax, in most cases due to infantile paralysis, but they were omitted from the study. In some of them the vital capacity gives little margin above the tidal air, and they suffer much from dyspnea. When the paralysis affected other muscles than those of the thorax, there was no indication of lowering of vital capacity, and such students were included.

4. *Dyspnea.*—The students in the group with low vital capacity are conscious of getting out of breath in ordinary life. Stairs are real obstacles, for they are often sadly out of breath on reaching the third floor office. Among them are some apparent exceptions, students who say they have no dyspnea, yet on further questioning say, "I never run." One student was kept out of the glee club because it was impossible for her to hold her breath long enough for the usual musical phrasing. Many suffer much in running, and in swimming they are held up for lack of "wind." A few seem not to suffer at all. Why do they not? They show persistently low vital capacity by all tests, yet they swim and they play at least moderately active games with no sense of limitation.

and home physicians, was to ask if the student had ever been cautioned not to overdo physically, especially after an infectious disease.

4. History of dyspnea.

5. History during college years. Participation in sports at college and during the summers.

6. General health status in college and from physicians' records.

7. Change in vital capacity in college years. Special class in 1929-1930 for students with low vital capacity.

For purposes of comparison this group of 85 students with low vital capacity was checked continually with the students who were 15 per cent or more above the average for their height (see chart 1, this issue, p. 933). This group totaled 121, being more numerous because the distribution curve for vital capacities appears to be somewhat skew. This skewness may easily be related to athletic sports.

The first thing to be said regarding the results of the study is that all the students 15 per cent or more below the average do not show signs of present or past disease, contrary to the implication of the quotation from Dreyer with which this paper began. However, the second thing to be said is that there is a conspicuous difference between these students with low vital capacity and the average college group. The results are discussed briefly under the headings outlined. A table and notes will add further details.

RESULTS

1. *Precollege History of Activity*.—The students with high vital capacity were athletic; they joined in the sports of their preparatory schools, in the vigorous life of summer camps and in informal sports in their homes. The students with low vital capacity were in the main "quiet little girls"—there were few sports in either their school or summer histories. The reasons for this quiet life vary from real physical handicap, which was frequently found, to family influence, "My mother is afraid of the water," or to place of living, "I grew up in the Canal Zone; it's hot there!" or to lack of a school program.

Special mention should be made of swimming, which is by far the most conspicuous sport of students with a high vital capacity and of which many of those with low vital capacity know little or nothing. The former swim long distances, dive and swim under water; if the latter swim at all, they are hindered by being winded, or they swim very short distances. The importance of swimming was not recognized when this study was first begun, so the data for the first two classes are incomplete.

2. *Special Activities*.—Of the students with high vital capacity, four play on wind instruments, with years of practice behind them, two on the trumpet, one on the slide trombone and one on the clarinet; three

7. *Change in Vital Capacity During College Years.*—For the entire group of 199 in the class of 1929 for whom determinations made during the freshman and senior years were available, the average increase was only 100 cc., scarcely any amount beyond the range of error. It thus appears that freshman standards may be considered suitable for adult young women. The students with high vital capacity change but little; practically none of them lose their high rating even though their activity may be very small after the college requirement in exercise is completed at the end of the sophomore year. Of a total of twenty-one students with low vital capacity who were followed through the four years, ten gained on the average 410 cc., an amount well above the general average for their classes. For these students there was no special program other than a general exhortation, when they came in for conference, on the benefits of sports. Four of this group lost an average of 260 cc. without known reason. The others showed no change.

Since it was apparent that at least some of this group with low vital capacity showed an increase, a special study was made of the group with low vital capacity of the fall of 1929, and twenty-five students were selected for special work in thoracic development and mobility under the direction of Miss Lillian Kuester, director of medical gymnastics at Mount Holyoke. Three of these students failed to report. The members of the group were given directions for suitable exercises, and were to report at intervals for conference and checking progress. The diligence of the group varied, but at the end of the year the results were these:

Total number	22
No change beyond ± 200 cc.....	11
Increase 210 to 400 cc.....	9
Average, 330 cc.	
Increase 410 cc. or more.....	2
Average, 600 cc.	

Of the eleven who did not gain, the reason for three may lie in pneumonia in the past and for one in a persistent cardiac limitation. Four reported only a few times and probably did not follow the program of exercise. There is no apparent reason for three, except that all had had little sturdy exercise in precollege days. The remark of one, "Mother was afraid of the water," is typical of the lack of appreciation of the value of sports in their homes. Of the eleven who showed good gains, two had had pneumonia, one had a persistent cardiac condition, and one was probably helped by an operation on her nasal septum which removed an obstacle to free breathing. But in the other cases we seemed to have the simple effect of a healthful reaction to wisely prescribed exercises. Several of these students reported a lessening of dyspnea, and, as they say, "more pep."

A careful study of this group would be of much interest, but there are few of them to study, not more than one or two a year.

Students in the group with high vital capacity suffer little from dyspnea except when participating in active sports like soccer and hockey or in fast swimming.

5. *College History: Sports.*—In the fall of the freshman year the first class teams show a marked preponderance of students with high vital capacity, though the basis of choice is success in playing the games. This preponderance continues throughout the college years. It is to be said, of course, that this group includes the long of limb and the broad-shouldered, students of past experience and success in the sports concerned, and one may be tempted to mix cause and effect. The students with low vital capacity are seldom found on class teams in the running sports, though a few appear in archery, volley ball and the like.

Many of the students high in vital capacity, but almost none of those low in vital capacity, are camp councillors during college years.

6. *College Health Status.*—One of the most interesting phases of this study was the rating of these two groups by the college physicians. Mount Holyoke is a residence college in a small town. The college medical department knows the medical history of each student rather fully, since contacts with outside physicians and specialists are made through the medical office. The physicians were asked to grade all members of these groups by this scale, A, excellent; B, good; C, fair; D, poor, a college health risk. The results surprised us by their clearness. The typical grade for the low vital capacity group is C, that for the high vital capacity group, A or B. In many cases the A's had never been mentioned in the college case histories.

In this connection the nutritional figures are of interest, though in the absence of standards that recognize varying widths of build as well as heights, we feel a lack of security in our results. They have not been tabulated, but there is no doubt of their general tenor. The girl with high vital capacity is not underweight—she is about what she should be for her build, or slightly overweight. The group with low vital capacity includes a large proportion of students who are markedly underweight and a few who are conspicuously overweight. The girls with high vital capacity are about 2.5 cm. taller than those with low vital capacity. The complete reasons for these differences are not known, but a future problem will be to consider the prevalence of healed rickets in the latter group. Their histories do not state whether they had rickets as babies or not; in fact, they do not know, but in several instances there is the high sternum to indicate thoracic involvement in babyhood. A further study is planned from this point of view.

TABLE 1.—*Comparison of Students Whose Vital Capacity Is More Than 15 Per Cent Above the Average for Their Height With the Group More Than 15 Per Cent Below the Average**

	Vital Capacity More Than 15 per Cent High	Vital Capacity More Than 15 per Cent Low
Precollege sports †.....	Total 118	Total 84
Athletic.....	61.8%	10.7%
Nonathletic.....	38.2%	89.3%
Swimming †.....	Total 111	Total 72
Much.....	82.0%	39.0%
Not much.....	16.2%	40.2%
None.....	1.8%	20.8%
Previous diseases		
Pneumonia.....	15 students	12 students
Pleurisy.....	1	3
Heart limitation past or present.....	4	10
Rapid heart.....	1	2
Rheumatism.....	1	1
Tires easily §.....	1	9
History of dyspnea.....	Total 108	Total 84
Marked.....	7.4%	44.0%
In sports only.....	20.4%	33.4%
Not troubled.....	72.2%	22.6%
On college athletic teams #.....	90 instances	13 instances
College health rating ¶.....	Total 121	Total 84
A, excellent.....	38%	1.2%
B, good.....	53%	22.6%
C, fair.....	9%	72.5%
D, college risk.....	0	3.6%

* There are 121 students with high vital capacity and 85 with low vital capacity. Since the completeness of the records and the time in college varies, the total for each point studied is not always the entire number; however, when it differs from the whole number it is so stated. Since the number of students with high and low vital capacity is not the same, the results are frequently given in percentages rather than in actual numbers.

† "Athletic" indicates great participation in active school sports, nearly always membership on teams, frequent summers in camp, etc. "Nonathletic" means absence of the foregoing activities and slight activity in home or school life.

‡ The differences in the figures are obvious, but the real differences are still greater. The students who swim "much" in the high vital capacity group often swim a mile or more, dive, swim under water etc. Anything above 100 yards, if the swimming was frequent, was included in this group. Many of the students with low vital capacity can swim hardly more than this distance; "lack of wind" is often their limiting condition.

§ The parent or home physician often gives suggestive notes on the entrance blank. These comments are the ones meant here, not observation after college is reached.

Each student may be a member of a team in more than one year. She may also play on more than one team during the year, one in the fall, one in spring. Only the students who make the first class teams are included, not those on the substitute teams.

¶ Rating made by the college physicians.

TABLE 2.—*Academic Standing and Academic and Social Honors of Students with High and Low Vital Capacity**

	High Vital Capacity	Low Vital Capacity
Academic average.....	81.19	79.39
Rank in class (highest student is no. 1), see text.....	114.5	138.0
Included in first 50 of the class.....	22	7
Included in lowest 50 of the class.....	12	16
Special academic honors (see text).....	15	2†
Major offices (filled by student election).....	15	2‡

* This study includes four classes, one for four years, one for three, and one for two, one for only one year. There were 87 students with high vital capacity and 56 with low vital capacity.

† One of the two students with low vital capacity having special academic honors is well-set up physically, though she is not athletic. Her vital capacity has increased by 400 cc. since she came to college two years ago, which takes her out of the low vital capacity class. She has a history of pneumonia in 1927, with probably a cardiac complication from which she may have been making a slow recovery. The other student is a typical student with low vital capacity in lack of exercise, poor color, poor posture and health record. Her vital capacity has not changed significantly in her three years of inactive college life.

‡ One of the two students having a major student office has none of the earmarks of low vital capacity. She plays games, she is the picture of health, she has a fine record academically and will doubtless take honors later on. Her vital capacity has increased by 360 cc. in her two years of college which takes her just above the 15 per cent low line. The other student is also successful in games and has a good health record, though she is no academic light. Her vital capacity is remaining about the same. Both these students evidently compensate in some way for the limitation they have in vital capacity.

The training of students with low vital capacity in thoracic development and mobility will be continued in the next years until we have surer basis for judgment. At present, the indication is that many of our students with low vital capacity are so hampered, not because of any involvement by disease, but simply because they were cheated of their heritage through a life of too little sturdy exercise. The evidence points to the years of adolescence as the best time for such training, and the fact that many of our students with high vital capacity were for two years with little sturdy exercise in the last part of their college course shows that the power once gained is not readily lost. The question is not answered as to how far special training in college years, coupled with a gradually increasing participation in sports, may serve to raise vital capacity to a height associated with safety if not with athletic prowess. Thus far it appears that we have a good lead to follow in helping this group of physically deficient students to surer health.

There is no thought in this study that vital capacity has any magic relation to health, but merely that we have here one measurable function which is a part of the complex indicating an oxygen supply and delivery adequate for the needs of the body in strenuous exercise as well as in the quieter parts of the day's program. The material just described is summarized in more definite form in table 1.

Certain other matters are of interest, notably the comparative academic success in the two groups with which we are concerned. The average grades of the high and low vital capacity groups are given in table 2. Each successive class has shown this difference, which, though not very great, is undoubtedly of significance. The students at Mount Holyoke are given numbers which indicate their relative academic rank in their classes, the highest student in the class being ranked no. 1 and so on. The total number in a class is about 270. These average ranks of the high and low vital capacity group are included in table 2 and also the number of each group in the highest and lowest fifty students of the class. These records are based on as much of the students' work as was available during the spring of 1930, for one class four years, for a second three years, and so on. The present freshman class was not used at all. Whatever method is used, the result is the same, the students with high vital capacity are more successful academically though high vital capacity works no academic miracles.

There are several types of "honors," the giving of the degree with honor, honor scholars in the sophomore year, special prizes of various kinds. The greater success of the high vital capacity group is shown by this mode of judgment also.

THYROTOXICOSIS FOLLOWING SUBTOTAL THYROID-ECTOMY FOR EXOPHTHALMIC GOITER*

WILLARD OWEN THOMPSON, M.D.

CHICAGO

ALBERT E. MORRIS, M.D.

BOSTON

AND

PHEBE K. THOMPSON, M.D.

CHICAGO

Subtotal thyroidectomy for exophthalmic goiter is in general a remarkably successful operation. In most cases it is followed by a prompt and permanent drop in the basal metabolic rate to normal, and practically a complete disappearance of symptoms. However, in some instances the results are not so satisfactory. Either the thyrotoxicosis, although diminished, is not abolished, or else it disappears only to recur at a later date. The scarcity of accurate information in the literature with regard to the frequency, duration, types and causes of post-operative thyrotoxicosis led us to undertake the present study. It is an analysis of 190 unselected cases of exophthalmic goiter in which subtotal thyroidectomies were performed at the Massachusetts General Hospital during the six-year period from Jan. 1, 1923, to Dec. 31, 1928, and were followed by determinations of basal metabolism and clinical examinations for from three months to six years after operation.

THE FOLLOW-UP

The total number of patients who underwent subtotal thyroidectomy for exophthalmic goiter during the six-year period from 1923 to 1929 was 266. Of these, 76 were followed for less than three months after operation, and were therefore not included in this study. The remaining 190 were followed in the manner described.

Method.—With rare exceptions, a determination of basal metabolism (using the Benedict-Roth apparatus and the Aub-DuBois standards) was made each time the patient was seen in the clinic. Following this determination, the patient was examined in the laboratory, usually by us. No attempt was made to follow patients by letter.

* Submitted for publication, May 26, 1930.

* All of these data were collected in the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital. The expenses of preparation of the manuscript were borne in part by Rush Medical College.

There are each year about a dozen major senior offices to which students are elected by their fellow students. There are but few junior offices, and still fewer sophomore and freshman opportunities for this type of distinction. The number of such posts held by the high and low vital capacity groups is stated in table 2.

SUMMARY

A comparative study of students whose vital capacity was more than 15 per cent above or below the average for their heights was made to determine whether the group with low vital capacity showed signs of disease and whether, also, there were indications that vital capacity is an important function for judging physical fitness. These students were found in five freshman classes at Mount Holyoke College; there were 121 with high vital capacity and 85 with low vital capacity. Two classes were studied for four years, with two conferences each year for each student. The other classes were studied for shorter periods, as their year of entrance made possible.

While in a few instances there seemed to be direct association of low vital capacity with past or present disease of the thorax, heart or lungs, the majority of these students seemed to be young women for whom the exercise program in the years previous to college was very limited. The response of twenty-two students in one class, which has been specially trained for thoracic development, was gratifying. By whatever test this low vital capacity group was tried out, by the test of general health, of academic or of social success, it appears that it was truly at a disadvantage. There is thus the indication that vital capacity is a measurable function of significance in the general picture of the young women whose relative success in the field of health one is anxious to rate fairly. Two "morals" appear: one, the importance of sturdy exercise for girls, especially in their adolescent years, the other, the opportunity of bettering the low vital capacity and with it the general health of at least many of this group of students during their college years.

cardia, undue nervousness, case of fatigue and excessive sweating, the patient was not considered thyrotoxic.

In the 190 cases that were followed, 153 (80.5 per cent) of the patients appeared to be cured, that is, they showed no definite thyrotoxicosis or no more than doubtful transient signs of it following operation. However, 37 (19.5 per cent) showed definite signs and symptoms.¹ The incidence of postoperative thyrotoxicosis by years is given in table 1. A possible cause for the high incidence in 1928 (31.1 per cent) will be discussed later.

SEVERITY OF POSTOPERATIVE THYROTOXICOSIS

Although 37 of the 190 patients had thyrotoxicosis after the operation, they all showed symptomatic improvement with one exception (in

TABLE 1.—*Incidence of Postoperative Thyrotoxicosis by Years*

Year	Patients Followed	Patients Thyrotoxic after Operation	Patients Thyrotoxic after Operation, per Cent
1923.....	18	4	22.2
1924.....	28	4	14.3
1925.....	40	5	12.5
1926.....	37	6	16.2
1927.....	22	4	18.2
1928.....	45	14	31.1
Totals.....	190	37	
Average incidence of postoperative thyrotoxicosis.....			19.5

case 6397, chart 10). The postoperative thyrotoxicosis was mild in 56.8 per cent of the cases, moderately severe in 35.1 per cent and severe in 8.1 per cent; whereas in the same cases before operation the thyro-

1. We (Thompson, W. O., and Thompson, P. K.: Low Basal Metabolism Following Thyrotoxicosis: I. Temporary Type without Myxedema, with Special Reference to the Rôle of Iodine Therapy, *J. Clin. Investigation* 5:441, 1928) previously reported the cases of a few patients who showed increased nervousness and slight tachycardia, palpitation and tremor in spite of a normal basal metabolism, and in whom these signs and symptoms disappeared when iodine was administered and the basal metabolism dropped to a subnormal level. When the basal metabolism was low the patients appeared healthy and no myxedema could be detected. However, since in these patients the evidence on which the diagnosis was based may be questioned, we have not considered them thyrotoxic in this study, with the exception of the patient in case 1812 (chart 3) in whom the basal metabolism eventually rose as high as plus 19 per cent when iodine was not being administered, and in whom there was no doubt about the presence of the disease. In other words, while we are well aware that the intensity of the thyrotoxicosis and the amount of elevation of the basal metabolism do not necessarily parallel one another, we felt that we should include in our criteria for the presence or absence of thyrotoxicosis one objective symptom that could not be questioned, that is, a persistently elevated rate of basal metabolism.

Duration of Follow-Up.—In these 190 cases, the patients were followed for the following periods: three months to one year after operation in 75 cases, between one and two years in 36 cases, between two and three years in 33 cases, between three and four years in 20 cases, between four and five years in 19 cases, and between five and six years in 7 cases.

Frequency of Follow-Up.—The patients (37 in all) with postoperative thyrotoxicosis were followed thus: in 12 cases, once a month almost continuously for from four months to four and three-fourths years, including 3 cases followed for three, four and one-fourth and four and three-fourths years after operation; in 6 cases, once a month for from one and one-fourth to six and one-half years, with gaps of eight months to three and one-half years; in 14 cases, every two to three months with a few omissions for from five months to four and three-fourths years (this includes 5 cases followed two and one-half, 3, three and two-thirds, four and four and three-fourths years after operation); in 3 cases, every two to three months for from two to five years, with gaps of from one to one and one-half years, and in 2 cases, every three to six months for five and two-thirds and five and three-fourths years, with gaps of two and one-half and four and one-half years, respectively.

The 153 patients who were not thyrotoxic after operation were not followed so closely. However, about 55 were seen on an average of every one to three months; 10 of these for less than a year, and the other 45 for from one to four and one-half years after operation. The remaining 98 patients were seen at varying intervals, that is, every three or six months and then not again for a year or more, for as long as six years after operation.

TYPE OF OPERATION

The subtotal thyroidectomy was usually done in one stage, but in a few instances two hemithyroidectomies were performed a few months apart (15 patients in the postoperative nontoxic group and 7 patients in the postoperative toxic group).

According to the records, the subtotal thyroidectomies effected the removal of from two-thirds to nine-tenths of the thyroid gland. This, of course, does not give an accurate idea of the amount of tissue left in, as the glands varied so much in size. It was the practice of one of the surgeons doing the greatest number of thyroidectomies to leave in only from 1 to 4 Gm. of tissue on each side whenever possible, but he often unavoidably left more.

INCIDENCE OF THYROTOXICOSIS FOLLOWING SUBTOTAL THYROIDECTOMY

In some cases it was difficult to decide whether thyrotoxicosis was present. In many more patients than those included in the postoperative thyrotoxic group there was a slightly elevated basal metabolism at some time after operation (in general, plus or minus 15 per cent was taken as the normal range); but unless a high metabolism was persistent and was accompanied by definite clinical symptoms such as tachy-

toxicosis was mild in 5.4 per cent, moderately severe in 43.2 per cent and severe in 51.4 per cent. All of the patients resumed their usual occupations following operation, although under more or less of a handicap according to the severity of the symptoms. A summary of the determinations of the basal metabolism made in the 37 patients who were thyrotoxic following operation is given in table 2.

In 24 of the 36 patients who improved, the basal metabolism was considerably lower without medication after operation than before pre-operative treatment with iodine was begun. In 3 cases (cases 2632, 2759 and 4530) it was not possible to make this comparison because no determinations of basal metabolism had been made before the administration of iodine preceding operation, and in one case (case 3867) because no determination was made after operation at a time when iodine was not being administered. In 3 of 6 cases (cases 2375, 3437 and 4353) showing no reduction in the basal metabolism at times when the patient was not taking iodine after operation, and in 3 cases (cases 1915, 5596 and 6102) in which little reduction was noted, there was general improvement with gains in weight ranging from 3 to 7 Kg. Similar improvement with gain in weight but no reduction in basal metabolism was noted by Porter² following a hemithyroidectomy. Considering the 37 cases as a whole, the basal metabolism at the time of admission to the hospital averaged about plus 64 per cent, and after operation, when no iodine was being administered, it averaged about plus 40 per cent.³

CLASSIFICATION OF POSTOPERATIVE THYROTOXICOSIS ON THE BASIS OF TIME OF ONSET

It is important to determine whether the disease disappears after operation and then recurs, or whether it merely persists. The thyrotoxicosis was considered persistent when there was no evidence to show that it had disappeared temporarily at any time after operation except under the influence of iodine. The thyrotoxicosis was considered recurrent only when there was evidence to show that there was a period after operation when, without medication, it was not present. On this basis, 35 of the 37 patients had persistent and only 2 recurrent thyrotoxicosis. In one of these definite recurrences (case no. 2524) the

2. Porter, C. A.: Analysis of My End-Results in Thyroid Surgery, Surg. Gynec. Obst. **36**:621, 1923.

3. In each instance, omitting cases 2632, 2759, 3867 and 4530 in which no comparisons could be made, the figure used was the highest postoperative rate of basal metabolism during a period in which there was no treatment with iodine.

Summary of Post-Discharge Basal Metabolic Rates

Lab- ora- tory Num- ber	Patient	Age at Time of Opera- tion, Years	Basal Metabolic Rate at Time of Admis- sion to Hospital, per Cent Normal	Last Basal Metabolic Rate Before Opera- tion, per Cent Normal	Sur- geon	Basal Metabolic Rate at Time of Discharge from Hospital, per Cent Normal	See chart 3 See chart 5
1812	Mr. J. W.	39	+ 52	+44	Unknown	+ 9 (10)	+32 (88), +42 (205), +25 (426), +1* (459), +19* (524) pregnant, +37 (1360), +12* (1376), +7* (1403), +9 (1416), +6 (2093)
1915	Mr. F. L.	43	+ 67	+53	C	+36 (13)	+38 (49), +22 (200), +15* (231), x-rays, +37 (298), +22 (357), x-rays, +8 (378), -1 (1597), -5* (1688), +26* (taking desiccated thyroid [1750])
2031	Mrs. R. S. C.	34	+ 58	+15*	B	+48*(7)	See chart 8
2077	Mrs. K. T.	24	+ 71	+25*	B	+17*(10)	+20 (107), +8 (190), +9 (280), +2 (394), +20 (582), +33 (645), +8* (669)
2375	Mr. O. G.	29	+ 37	+19*	A	-11*(8)	+37 (77), +38 (258), +9* (349), +38 (524), +32* (583), +35* (604), left hemithyroidectomy (607), +24 (1662), +17* (1685), +14* (1825)
2524	Miss F. B.	39	+ 59	+29*	A	+ 6*(8)	+51 (58), +25 (92), +18* (123), +44 (107), x-rays, +42 (211), +36* (241), +63* (394) in hospital, +8* (403), second subtotal thyroidectomy (407), +1* (424), +28 (458), +29 (657), +9* (687), +3* (802), +27* (849), +16* (914), -4* (1089), -12* (1511), +5 (1649), -4 (1767)
2632	Miss G. A. O.	18	+ 40*	+31*	A	+ 5*(11)	+12* (46), +23 (145), +31* (173), +12* (202), +19* (754), +29 (1404), +9* (1463), +19* (1540), x-ray, +29 (1587)
2759	Mrs. A. P.	36	+ 40*	+25*	B	+10*(9)	-7* (40), +1* (108), +21 (142), +27 (253), +16* (289), +22* (491), +32 (527), x-rays, +12 (610), +35 (735), +16* (751), +10* (775), +16 (787), +19 (880), +11* (923), +23 (1008), +13* (1031), +9* (1108), +13* (1443)
3010	Mrs. N. P.	44	+ 60	+12*	G	-10*(13)	+5* (39), +22* (175), +15* (263), +34 (354), +34 (362), x-rays, +14 (423), +8 (606), +34 (671), +30 (804), +9* (920), 0* (1340)
3187	Mrs. M. L. P.	54	+ 80	+22*	G	+16*(9)	+30 (30), +8* (44), +45* (87), +44* (100), +62 (142) in hospital, +49* (154), second subtotal thyroidectomy (157), +1* (164), +40 (205), +10* (220), +39* (277)
3260	Miss B. S.	18	+119	+42*	A	- 2*(10)	See chart 9
3437	Mr. C. V.	15	+ 53	-11*	B	+20*(10)	+3* (38), unquestionably toxic (453)
3477	Mrs. M. C. S.	31	+ 64	+26*	A	+ 8*(7)	See chart 4
3807	Mrs. E. H.	30	+ 45	+20*	K	+ 5*(8)	+47 (22), +52* (87), +24* (179), +38 (198), x-rays, +48 (282), +7* (305), -3* (373), +22 (392), +22 (448), +5* (462), -3* (644), -1* (815), -22 (848), -2 (1072)
3913	Mrs. M. R.	23	+ 54	+31*	A	+21*(7)	+13 (38), +24 (166), +16 (171), +1* (185), +2* (193), +14 (218), -10* (290), +15 (613), +35 (783), +16 (874), +15* (916)
3961	Mrs. C. N.	29	+ 62	+21*	E	+19*(10)	+45 (738), +27* (762), +41* (837), +32* (870) in hospital, second subtotal thyroidectomy (871), +1* (878), -23* (958), -22 (972)
3967	Miss B. P.	15	+ 45	+ 9*	G & H	+ 5*(8)	+13 (29), +24 (171), -5* (188), -4 (195), +17 (209), +24 (780)
4353	Mrs. M. G.	43	+ 47	+22*	D	+16*(7)	+21* (36), +22 (366), +43 (653), +19* (695), +24* (818)
4421	Miss W. McL.	21	+ 39	+ 3*	H	- 6 (8)	+2* (64), +27 (150), +20 (151), -3* (189), -4* (273), -5* (517)
4530	Mr. M. O.	48	+ 44*	+34*	B	+ 7*(8)	+37 (36), +25 (64), +8* (84), +17* (148), +8* (200), +45 (231), +43 (235), +6* (263), +18* (350), +1* (508)
4694	Miss E. F.	28	+ 99	+34*	A	- 7*(10)	+13* (52), +27 (88), +26 (162), +16* (190), +9* (245), +8* (435), +19 (505), +28 (581)
5168	Mrs. E. H.	26	+ 81	+26*	B	+ 6*(13)	+35 (41), +33 (131), +16 (364), -2* (378), +5* (399), +20 (435), +27 (470), +15* (505), +27 (569)
5193	Mrs. V. P.	42	+ 64	+42*	A	+25*(8)	See chart 2
5203	Miss A. W.	22	+ 51	+52*	I	+28*(8)	See chart 7
5272	Miss E. M.	35	+103	+25*	D	+21 (14)	+34 (49), +27 (97), +23* (127), +41 (194), +13* (216), +27* (279), x-ray, +31* (385), +29* (419)
5281	Miss V. G.	18	+ 80	+42*	A	+ 9*(8)	+40 (46), +30 (100), 0* (125), +18* (212)
5396	Mr. H. E.	33	+ 54	+27*	B	+ 9*(25)	+42 (54), +30* (150), +7* (367), +17 (423)
5640	Mrs. M. E. B.	40	+ 36	+1*	B	-11*(10)	+9 (73), +34 (162), +42 (288), +19* (316)
5767	Mrs. J. P.	48	+ 88	+38*	J	+11*(10)	+45 (53), +24* (60), +24* (147), +37 (179), +44 (188), +13* (209), +53 (298), +22* (328), +27* (360)
5944	Mr. P. M.	42	+ 63	+41*	J	+36*(11)	+25 (47), +19 (54), +19* (83), +15* (185), +37 (206), +29 (210), +15* (231), +21* (321)
5957	Mrs. M. B.	37	+ 90	+28*	D	+17*(13)	+33* (49), +32* (75), +53 (106), +16* (148), +15* (183)
5995	Miss M. A. P.	17	+ 35	+13*	E	- 5*(10)	+23 (79), +12* (110)
6102	Mr. J. C.	40	+ 64	+65*	D	+20*(8)	+42 (50), +32 (76), +41 (147)
6125	Mrs. M. E. M.	23	+ 33	+14*	F	0*(8)	+15* (26), +11* (55), +23 (98), +30 (140), +27* (186), +18* (220)
6248	Mrs. M. C.	25	+ 71	+35*	A	+22*(7)	See chart 10
6376	Miss E. S.	21	+ 81	+26*	F	+ 4*(10)	
6397	Miss K. R.	26	+ 42	+15*	F	+ 8*(11)	

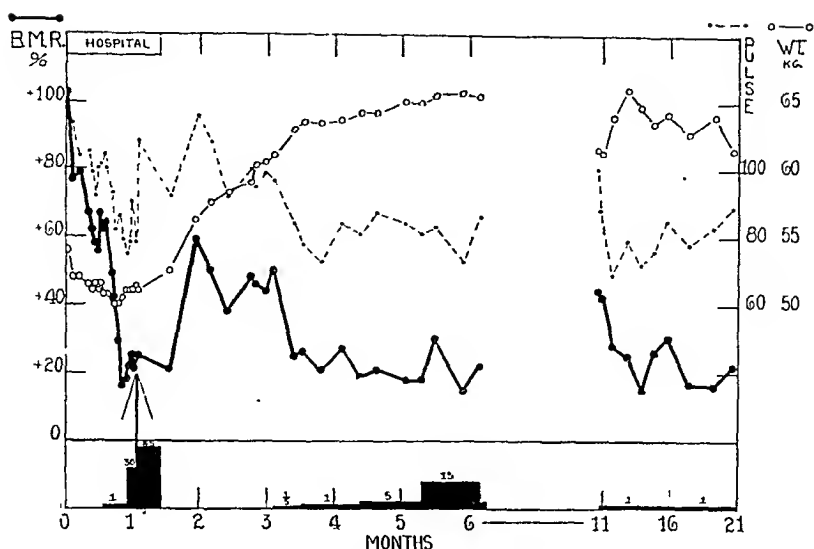


Chart 2 (lab. no. 5272).—Typical persistence of exophthalmic goiter following a subtotal thyroidectomy, showing the course of the basal metabolism, pulse and weight. Note that the level of the basal metabolism when iodine was not being administered was about the same ten months after operation as from one to two months after operation, and that the level to which it was depressed by iodine was the same twenty months after operation as two weeks after operation. This chart also shows that iodine may hold the basal metabolism at a constant level for many months.

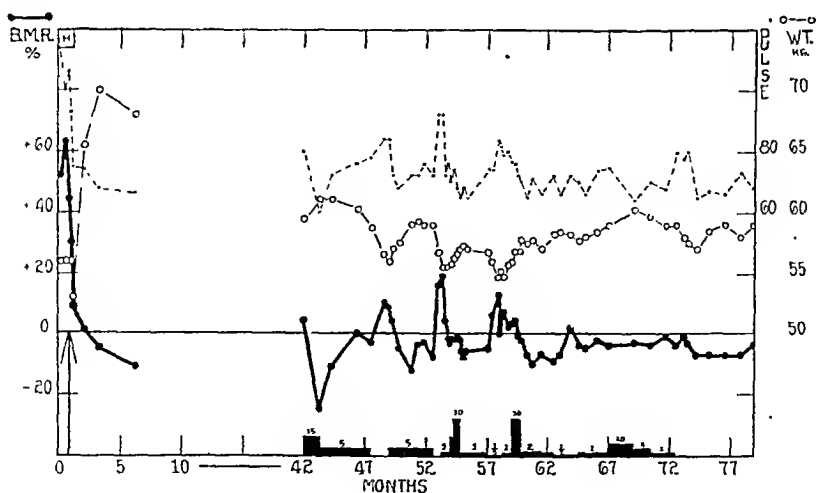


Chart 3 (lab. no. 1812).—Recurrence of exophthalmic goiter in association with regeneration of thyroid tissue, after the disease had been absent for at least five and one-half months following a subtotal thyroidectomy; and control of this thyrotoxicosis by iodine until it and the palpable thyroid tissue disappeared.

onset was between thirteen and nineteen months after operation, and in the other (case no. 1812), between five and one-half months and three and one-half years after operation (this patient was normal until five and one-half months after operation, but was not seen again until three and one-half years after operation, at which time thyrotoxicosis was present). Of the 35 patients in whom apparent persistences were observed, the high basal metabolism was first noted: in 15 cases, within two weeks after operation, usually at the time of discharge from the hospital; in 4 cases, between two weeks and one month after operation; in 10 cases, between one and two months; in 3 cases, between two and three months; in 2 cases, between three and four months, and in 1 case, between one and eight months.

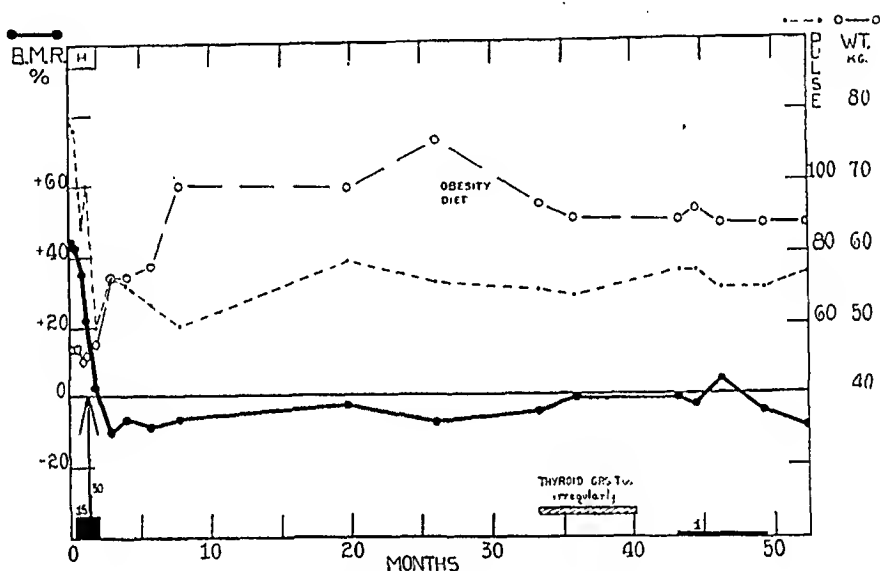


Chart 1 (lab. no. 3094).—The usual course of the basal metabolism, pulse and weight in a case of exophthalmic goiter cured by one subtotal thyroidectomy. Note that following operation the basal metabolism promptly dropped to normal and remained there. In this and subsequent charts, *H* denotes a period of hospitalization; the arrows denote subtotal thyroidectomies; the half-arrows, hemithyroidectomies; the black areas, periods of treatment with compound solution of iodine; the figures above them, the daily doses in drops, and the cross-hatched areas, periods of treatment with desiccated thyroid.

In the 20 cases of persistence in which the high basal metabolic rate was first noted later than two weeks after operation, there were usually a few intervening normal metabolic rates (table 2), but these were obtained while the patient was taking iodine. This medication with iodine renders it impossible to tell definitely whether or not these patients had a spontaneous brief interval of freedom from the disease. The prompt rise in the basal metabolism, however, after the omission of iodine, together with the presence of palpable thyroid tissue before its omission in many cases, makes it appear highly probable that such

was not the case. In any event, there were only 3 patients in whom the time of onset of the postoperative thyrotoxicosis was obscured for more than three months.

Data from a typical case in a patient who showed no postoperative thyrotoxicosis, in one with a typical persistence and in one with a typical recurrence are recorded in charts 1, 2 and 3, respectively.

In table 3 are contrasted the basal metabolic rates at the time of discharge from the hospital and during iodine administration of the 37 patients who were thyrotoxic following operation and 37 patients selected at random from the 153 who were not thyrotoxic following

TABLE 3.—*Comparison of Basal Metabolic Rates During Administration of Iodine Shortly After Operation in Patients Who Were Thyrotoxic and in Those Who Were Not**

Basal Metabolic Rate, per Cent Normal	Patients Not Thyrotoxic after Operation	Patients Thyrotoxic after Operation
+30 or over.....	..	2
+25 to +29.....	..	2
+20 to +24.....	..	5
+15 to +19.....	..	6
+10 to +14.....	2	2
+ 5 to + 9.....	6	10
0 to + 4.....	6	3
— 5 to — 1.....	8	2
—10 to — 6.....	14	3
—15 to —11.....	1	2
Total.....	37	37

* In the thyrotoxic group, one patient in the +20 to +24 division and another in the —10 to —6 division had omitted iodine for four and five days, respectively, before the observation was made. These are inadequate lengths of time for the effect of iodine to wear off. One patient in the +5 to +9 group did not have any iodine during the period of hospitalization, but the basal metabolism certainly would not have been any higher than this on iodine.

operation. Whereas in 15 (40.5 per cent) of the 37 patients who were thyrotoxic following operation, the basal metabolism was plus 15 per cent or higher at the time of discharge (usually from ten to fourteen days after operation) when iodine was being administered, in no case in the other series was it as high as plus 15 per cent under these conditions. In only 7 (19 per cent) of the thyrotoxic cases was it lower than 0 at the time of discharge, as compared with 23 (62 per cent) of the nontoxic patients. Although the data are not extensive enough to warrant definite conclusions, a similar situation appears to have existed in the patients undergoing subtotal thyroidectomy in the days before iodine was used, except that the basal metabolism in those that remained thyrotoxic did not return to normal until the disease disappeared spontaneously.

line CD and then rises, some regeneration of thyroid tissue can often be observed when it does rise. If the usual short, preoperative and postoperative courses of iodine are given, the metabolism may drop from a point A to a point X before operation. Then, if a cure results from thyroidectomy, it will follow the line XYO . If the disease persists, the course of the metabolism may lie anywhere between the lines XDO and $XYDO$; that is, it usually drops somewhat immediately after the operation, occasionally to a standard normal level. The subsequent rise usually follows the omission of iodine, and the line DO is intended to show the course of the metabolism when no iodine is being administered. If a recurrence takes place, then at any point P in the line YO (the line YP usually covering at least several months) the metabolism

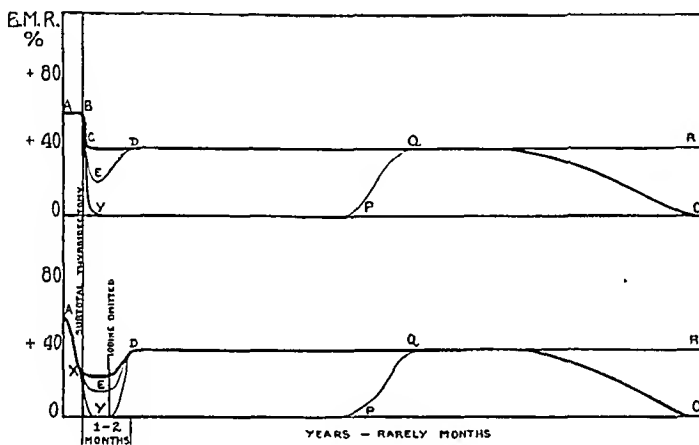


Chart 6.—Schematic course of the basal metabolic rate in persistence and recurrence of exophthalmic goiter, in patients who do not receive iodine (upper half of chart) and in those who do receive it for a short period before and after subtotal thyroidectomy (lower half of chart).

risks and may follow any course PQO . The line DQ has been extended to R to allow for occasional cases in which the disease seems to last indefinitely.

Several variations of the courses described may be noted; for example, the severity of the thyrotoxicosis following operation, as measured by the height of the rate of basal metabolism, varies considerably from patient to patient.

CAUSE OF POSTOPERATIVE THYROTOXICOSIS

Miscellaneous Factors.—It may be seen from tables 4 to 6 that the average age, age limits, age distribution, sex distribution and duration of the disease at the time of operation were about the same in the toxic as in the nontoxic group. Not only was the average initial basal metabolic rate roughly the same in the two groups of patients, but the

months in 3. While in the 5 cases in which it was possible to estimate the duration, the disease had disappeared within from one to four years after operation, its disappearance was apparently hastened by additional treatment in 3 of these, and the foregoing data show that it may often persist longer than this, for from four to six years, if not more, in at least 13 per cent of the cases (chart 5).

Duration of Recurrences.—In case 2524 the duration of the recurrence was unknown. The patient was observed for only two months without medication at the time the disease recurred.

In case 1812 (chart 3), the patient was free from symptoms and showed a normal metabolism for six months after iodine was last omitted. The recurrence lasted at least for from one to two and one-

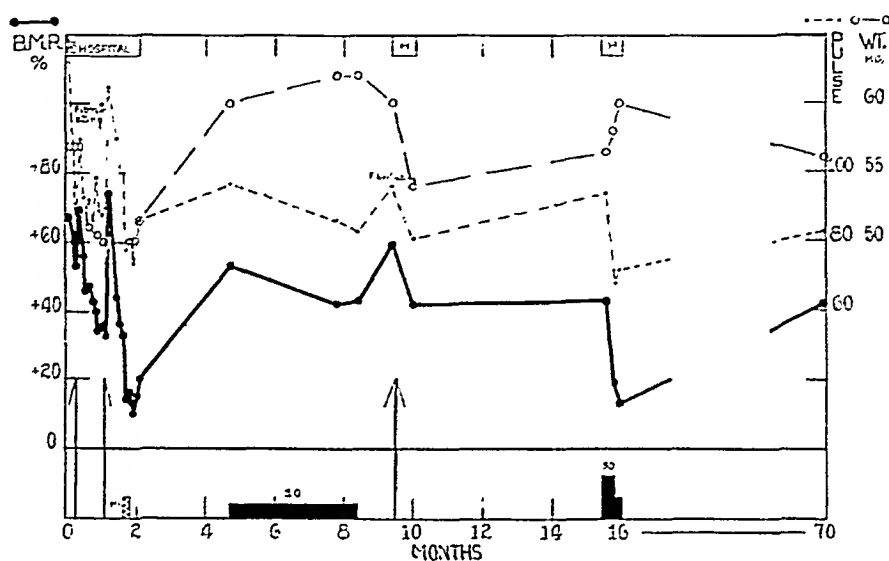


Chart 5 (lab. no. 1915).—Prolonged persistence of exophthalmic goiter and regeneration of thyroid tissue in spite of two hemithyroidectomies and one subtotal thyroidectomy for exophthalmic goiter.

half years while the patient was under observation, in addition to the unknown length of time it was present during the three year hiatus before he returned to the clinic for treatment.

SCHEMATIC REPRESENTATION OF PERSISTENCES AND RECURRENCES

From the foregoing data it is possible to construct a schematic representation of the various courses of the basal metabolism following subtotal thyroidectomy for exophthalmic goiter (chart 6). If no iodine is administered, the metabolism in the first few days after operation may drop from a point *B* to a point *C*. Then it may follow any one of several courses. If a cure results, it follows the line *CYO*. If the disease persists, the metabolism may follow any course between *CDO* and *CEDO*; that is, it almost never reaches a standard normal level until the disease disappears. If the metabolism drops much below the

TABLE 7.—*Basal Metabolic Rate on Admission to Hospital*

Basal Metabolic Rate,* per Cent Normal	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Below +40	7	18.9	39	25.5
+40 to +49.....	7	18.9	38	24.8
+50 to +59.....	7	18.9	31	20.3
+60 or over.....	16	43.3	45	29.4
	37		153	
Highest	+119 per cent		+102 per cent	
Lowest	+ 33 per cent		+ 15 per cent†	
Average	+ 58 per cent		+ 51 per cent	

* In a few cases this was during the administration of iodine.

† During the administration of iodine.

TABLE 8.—*Size of Thyroid Gland Before Operation (Incomplete)*

Size of Thyroid Gland	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Not enlarged	0	0.0	4	3.4
Slightly enlarged	5	15.2	21	18.1
Moderately enlarged	22	66.6	82	70.7
Markedly enlarged	6	18.2	9	7.8
	33		116	

TABLE 9.—*Bruit Over Thyroid Gland Before Operation (Incomplete)*

	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Bruit	33	100.0	93	80.2
No bruit	0	0.0	23	19.8
	33		116	

TABLE 10.—*Amount of Thyroid Tissue Palpable After Operation*

	Patients Thyrotoxic after Operation		Patients Not Thyrotoxic after Operation	
	Number	Per Cent	Number	Per Cent
Note was made in.....	35		104	
Palpable tissue absent.....	1	2.9	45	43.3
Palpable tissue present.....	34	97.1	59	56.7
Questionable amount	4	11.4	26	25.0
Definite amount	17	48.6	23	26.9
Considerable amount	13	37.1	5	4.8

level to which iodine depressed the rate of basal metabolism before operation was also roughly the same in both. A somewhat higher percentage of cases in the postoperative toxic group was found to have an initial basal metabolism of plus 60 per cent or over, a markedly

TABLE 4.—*Age of Patient at Time of Operation*

Age	Patients Thyrototoxic after Operation		Patients Not Thyrototoxic after Operation	
	Number	Per Cent	Number	Per Cent
Under 20 years.....	5	13.5	19	12.5
20 to 29 years.....	12	35.2	36	23.7
30 to 39 years.....	9	24.3	46	20.3
40 to 49 years.....	9	24.3	39	25.6
50 to 59 years.....	1	2.7	11	7.2
60 years or over.....	0	0.0	1	0.7
	37		152	
			1 unknown	
Average age	30.5 years		30.6 years	
Oldest	54 years		68 years	
Youngest	15 years		14 years	

TABLE 5.—*Sex of Patient*

Sex	Patients Thyrototoxic after Operation		Patients Not Thyrototoxic after Operation	
	Number	Per Cent	Number	Per Cent
Male	9	24.3	34	22.2
Female	28	75.7	119	77.8
	37		153	

TABLE 6.—*Duration of Disease at Time of Operation*

Duration	Patients Thyrototoxic after Operation		Patients Not Thyrototoxic after Operation	
	Number	Per Cent	Number	Per Cent
Six months or less.....	11	29.7	52	34.0
Between six months and one year.....	11	29.7	47	30.7
Between one year and two years.....	4	10.8	23	15.0
Over two years.....	10	27.0	21	13.7
Unknown	1	2.7	10	6.6
	37		153	
Shortest duration	1 month		3 weeks	
Longest duration	5 years		15 years	
Average duration	18.8 months		18.7 months	

enlarged thyroid before operation, and a bruit⁴ over the gland before operation (tables 7 to 9).. Apart from these slight differences, there were no definite distinctions between the two types of patients.

4. It is of interest that in patients who are thyrotoxic following a thyroidectomy, a bruit over the thyroid is less common than before operation, owing, no doubt, to the changes in blood supply resulting from the operation.

Preoperative and Postoperative Administration of Iodine.—One of the surgeons had the impression that postoperative thyrotoxicosis has become much more common since the preoperative use of iodine. Consequently, in table 12 we have compiled the data on the patients undergoing subtotal thyroidectomy before this medication came into vogue.

TABLE 11.—*Incidence of Postoperative Thyrotoxicosis According to Surgeons*

Surgeon	Patients Operated On	Patients Thyrotoxic After Operation	
		Number	Per Cent
A	85	11	12.9
B	42	8	19.0
C	19	1	5.3
D	10	4	40.0
E	8	2	25.0
F	8	3	37.5
G	5.5	2.5	45.4
H	4.5	1.5	33.3
I	3	1	33.3
J	2	2	100.0
K	1	1	100.0
L	1	0	0.0
Unknown	1	0	0.0
All surgeons	190	37	19.5
Surgeons A, B and C*.....	146	20	13.7
The remaining 10 other surgeons.....	44	17	38.6

* C, a thyroid surgeon, who retired shortly after the present study began, had done a large number of thyroidectomies before 1923.

TABLE 12.—*Incidence of Thyrotoxicosis Following Subtotal Thyroidectomy Before 1923,* According to Surgeons*

Surgeon†	Patients Followed for 3 Months or More After Operation	Patients Thyrotoxic After Operation	
		Number	Per Cent
C	21	4	19.1
A	19	2	10.5
K	1	1	100.0
Totals	41	7	
Average incidence			17.1

* That is, before the use of iodine.

† If tables 11 and 12 are combined, the percentages of recurrences for A and C are equal.

As may be seen, the percentage of postoperative thyrotoxicosis before the days of the use of iodine was 17.1 as compared with 19.5 since the introduction of iodine. The majority of the foregoing operations were performed by two of the three surgeons (A and C) who now have the smallest number of persistences. It appears, therefore, that preoperative medication with iodine is not a determining factor.

Practically all of the patients received iodine postoperatively for at least a week, that is, until discharge from the hospital, and many of

Palpable Thyroid Tissue After Operation.—In most of the cases of postoperative thyrotoxicosis palpable thyroid tissue was present. The amount was estimated rather roughly by palpation, and is expressed in table 10 by the terms questionable, definite and considerable. In the “questionable” cases the thyroid tissue was sufficiently difficult to palpate to render its presence open to question. In the “definite” cases the thyroid tissue could be felt without difficulty and varied in amount up to 1.5 cm. in diameter. The “considerable” cases included all those in which there was a mass of 1.5 cm. in diameter or larger. Within the first one to two months after operation, palpation is often not especially valuable because of the induration about the scar. In many instances a definite amount of palpable tissue probably did not represent regeneration, but simply the tissue left by the surgeon; nevertheless there was unquestionably regeneration in many of the patients with a “considerable” amount of tissue. In some of the patients the amount of palpable tissue increased in size during observation. This regeneration began shortly after operation and did not represent a true recurrence, but simply an effect of the persistence of the cause of the disease. A small amount of tissue could be felt in many of the postoperative nontoxic cases as well as in the toxic cases, but a “considerable” amount was almost always associated with thyrotoxicosis. Thyrotoxicosis without palpable thyroid tissue is occasionally encountered following thyroidectomy, but it is rare in our experience, only one mild case (case 3187) being noted in this series.

Amount of Tissue Left in at Operation.—The amount of tissue left in at operation was practically impossible to determine with any degree of accuracy, as in many cases the surgeon did not attempt to state in his operative notes the fraction removed, calling the operation simply a “subtotal thyroidectomy”; and even in cases in which the fraction was expressed, it was admittedly only a rough approximation. Therefore, instead of attempting to tabulate the amount of tissue left in situ, we tabulated the results of the individual surgeons in table 11. It may be noted that the combined results of the three surgeons who had performed the greatest number of thyroidectomies are definitely better than the combined results of ten other surgeons, each of whom had performed relatively few thyroidectomies. The percentage of cases of postoperative thyrotoxicosis was 14.4 for the first three surgeons and 36.3 for the ten others. We know from observation that the three surgeons who had the smallest incidence had performed more complete thyroidectomies than the others. It is fairly evident that experience in performing the operation is an important factor in preventing postoperative thyrotoxicosis.

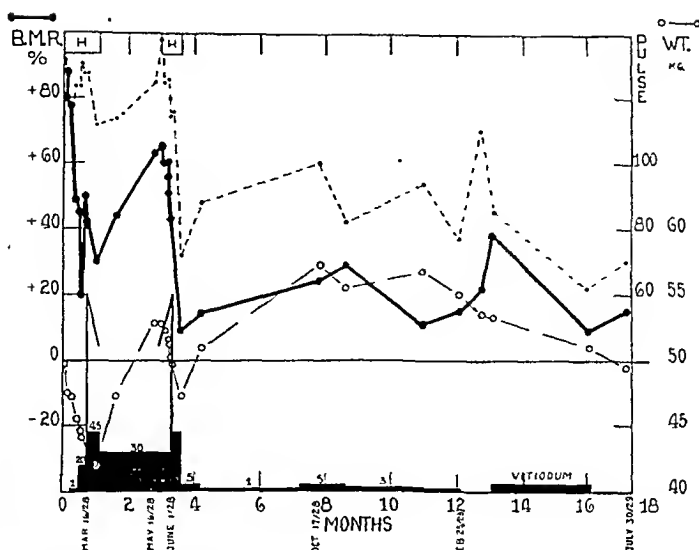


Chart 7 (lab. no. 5581).—Failure of two extensive hemithyroidectomies to reduce the basal metabolic rate to normal in a case of exophthalmic goiter. There was marked regeneration of thyroid tissue following each operation. The thyrotoxicosis was controlled for fairly long periods by iodine.

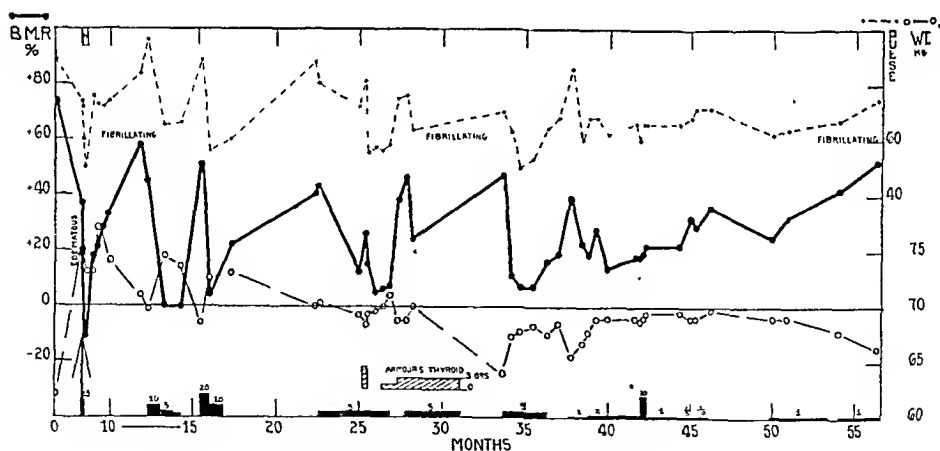


Chart 8 (lab. no. 2375).—Progressive, but gradual (years) increase in the level to which iodine depressed the high basal metabolism that persisted following a subtotal thyroidectomy for exophthalmic goiter. Some of this increase may be accounted for by a rather marked regeneration of thyroid tissue.

them received it continuously for several weeks thereafter. Many others received it intermittently shortly after discharge. In some of the toxic cases the postoperative thyrotoxicosis was first evident only after a continuous postoperative course of iodine for from one to four months had been omitted, although its presence often seemed obvious before this because of the large amount of palpable thyroid tissue. In most of the other toxic cases, it was evident at the time of the first postoperative basal metabolism determination, in spite of treatment with iodine. Thus the postoperative administration of iodine does not prevent the occurrence of thyrotoxicosis nor the regeneration of thyroid tissue.

TREATMENT, INCLUDING THE RESPONSE TO IODINE

Most of the patients received iodine at least intermittently after operation. In 10 cases its use was not continued long enough to determine the patient's response. In 3 of the remaining 27 cases little or no reduction in basal metabolism was noted during its administration, and in 3 others, only a temporary reduction. In 18 of the remaining 21 cases the basal metabolism could be held at a more or less constant level for from months to years by continuous administration. In 11 of these the level to which iodine thus depressed the metabolism was plus 15 per cent or lower; in 6, from plus 16 to plus 20 per cent, and in 1 case, from plus 21 to plus 25 per cent.⁵ In three cases the level to which iodine reduced the basal metabolism was somewhat inconstant and ranged between zero and plus 33 per cent. In general, the signs and symptoms of the disease in patients in whom iodine held the metabolism at a level of plus 15 to plus 25 per cent were only slight. In all cases showing only temporary improvement or none during the administration of iodine, there was a large amount of palpable thyroid tissue. Various types of response to iodine are shown in charts 2 to 5 and 7 to 10.

In 6 cases a second operation was performed, with varying degrees of relief (usually complete). A second operation was recommended in 4 other cases; in 3 it was refused and in the fourth it is to be done soon. Roentgen treatment was given in 7 cases, with some improvement in 5.

5. The fact that in fifteen of the patients who were thyrotoxic following operation the basal metabolism was plus 15 per cent or higher during the administration of iodine at the time of discharge from the hospital (table 3) is directly related to the fact that in at least an equal number of patients, iodine did not hold the rate of basal metabolism constantly below plus 15 per cent after discharge. In a few patients, the level at which iodine held the basal metabolism was a little higher following than at the time of discharge. This slight rise could be attributed to the elimination of rest, to a diminution in the effect of iodine or to an increase in the severity of the disease. All three were probably factors.

RESULTS OF SUBTOTAL THYROIDECTOMY FOR EXOPHTHALMIC GOITER
IN VARIOUS CLINICS

The type of follow-up that includes both physical examination and the determination of the basal metabolism at fairly frequent intervals is essential to procure accurate information regarding the results of subtotal thyroidectomy for exophthalmic goiter. Unfortunately, many of the reports in the literature of the percentage of cures obtained with this form of treatment are based on a follow-up by letter or by one physical examination, and sometimes only on the condition of the patient at the time of discharge from the hospital. Such reports are prone to show too high a percentage of cures. Similar methods applied to our series would indicate fewer toxic cases. It is remarkable in some instances how consistently high the basal metabolism may be after operation (about plus 40 per cent) and yet be associated with signs and symptoms of only mild thyrotoxicosis (in cases 5272 [chart 2] and 5944). Such patients often have few subjective symptoms and gain considerable weight, yet there are definite signs of the persistence of the disease that can be detected by careful observation.⁶ Richter⁷ remarked on the cases of 6 such patients in his series, who, in their own estimation, might have been reported as cured. Then, if we had seen our patients only once several years after operation, some of the cases in which the disease persisted for a time and then disappeared would have been missed. Figures based on the condition of the patient a week or two after operation would be almost worthless, because our patients, according to the routine followed in most clinics, were given iodine during the postoperative period in the hospital, which lasted about two weeks.

Elliott,⁸ in 1926, from the Wesley Memorial Hospital, Chicago, reported on the recalling of 100 patients with hyperthyroidism (including 62 with exophthalmic goiter) on whom subtotal thyroidectomy had been performed from six months to six years before the recall. The rate of basal metabolism was determined in 72 cases. In 50 it was normal, in 9 it was minus 10 per cent or lower, and in 13 it was plus 10 per cent or higher. However, of the 70 who considered themselves

6. Careful questioning and observation show that such patients present some or all of the following signs and symptoms: increased nervousness, emotional instability, insomnia, increased perspiration, palpitation, tachycardia and tremor. Compared with their preoperative state, the improvement in these patients is sometimes so marked that they consider themselves well. After treatment with iodine, however, they usually notice a further marked improvement.

7. Richter, H. M.: Thyroidectomy: Its Relation to the Cure of Thyrotoxicosis, *J. A. M. A.* **88**:888 (March 19) 1927.

8. Elliott, C. A.: The Control of Hyperthyroidism by Thyroidectomy: Results in One Hundred Cases, *J. A. M. A.* **89**:519 (Aug. 13) 1927.

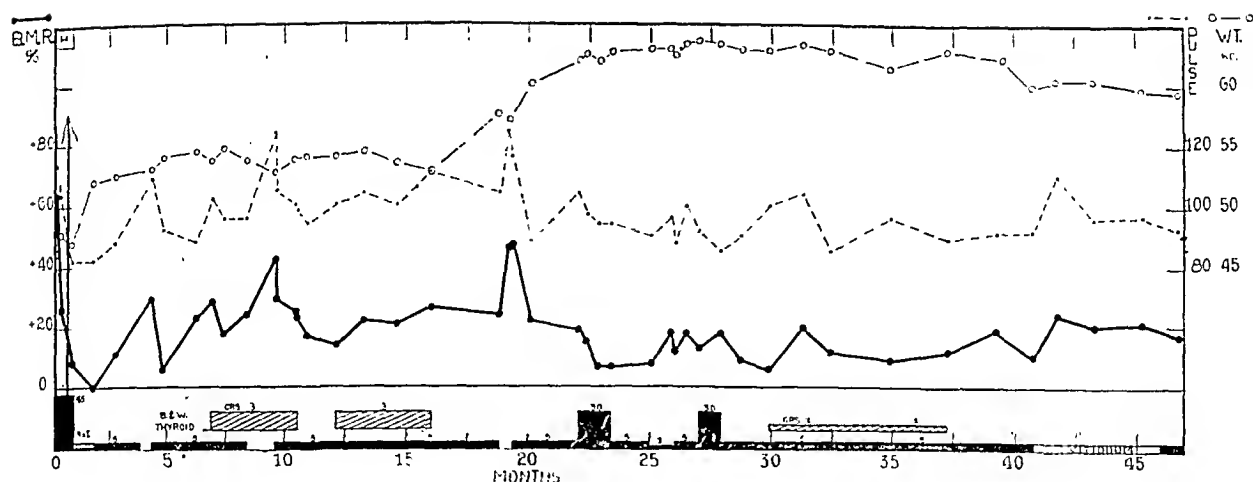


Chart 9 (lab. no. 3477).—Typical persistence of exophthalmic goiter after subtotal thyroidectomy, with control of the thyrotoxicosis by iodine continuously for four years after operation, except during three short omissions of that medication. The patient married and was able to do housework and private nursing during the period of observation, but some symptoms and signs of the disease were present, in addition to a large amount of palpable thyroid tissue. A second operation was therefore advised, and the patient finally consented.

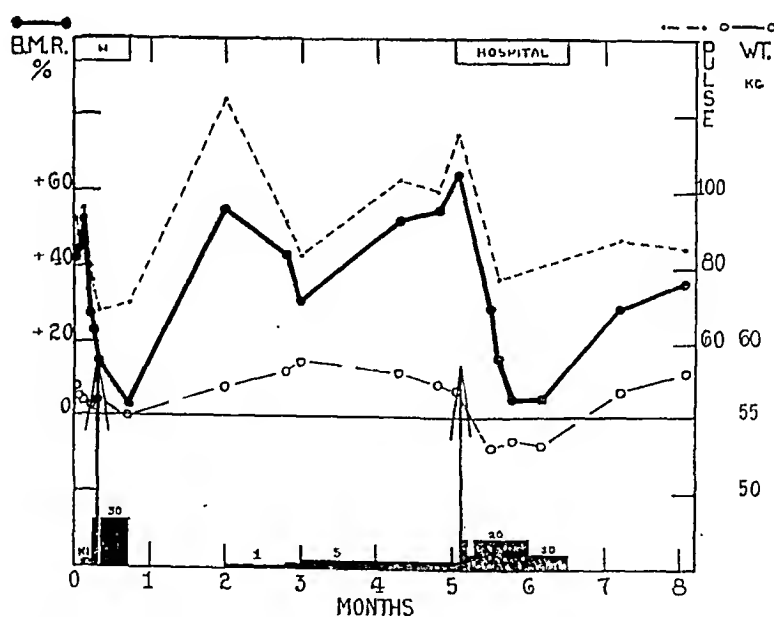


Chart 10 (lab. no. 6397).—Typical persistence of exophthalmic goiter in spite of two subtotal thyroidectomies, with only temporary improvement during the administration of iodine. Marked regeneration of thyroid tissue was noted following each operation.

Lahey Clinic, noted that 6.7 per cent of their patients with exophthalmic goiter failed to show a normal basal metabolism six months after subtotal thyroidectomy. Smith, Clute and Strieder,¹⁴ in 1928, at the same clinic, in following 100 cases of hyperthyroidism by physical examination and determinations of basal metabolism for one year or more after subtotal thyroidectomy observed 7 patients with persistence of the disease. Kessel and Hyman¹⁵ of New York, in 1927, reporting results in 60 cases of exophthalmic goiter two years after subtotal thyroidectomy, said that 15 patients had marked exacerbations at one time or another after operation and 18 others had mild residual symptoms. In only 7, however, was the basal metabolic rate higher than plus 18 per cent at the last reading. Mason¹⁶ of Seattle, in 1920, in a follow-up by letter in 42 cases of subtotal thyroidectomy for exophthalmic goiter, found a second operation necessary in 12 per cent. Waits,¹⁷ in 1922, in a letter follow-up from one to six years after operation (usually subtotal) for exophthalmic goiter, said that 11 per cent of the patients who answered had a "slight return of goiter." One of the patients had a second operation. Brodersen and Harbitz,¹⁸ in 1927, reported 87.4 per cent of the patients cured, 11.5 per cent improved and 1.1 per cent worse, from one to four years after subtotal thyroidectomy for exophthalmic goiter; 5.7 per cent had undoubted or questionable relapses. Ladwig,¹⁹ in 1925, had good results in 21 of 35 cases, fair in 6

1924), on the basis of a follow-up by letter, reported an incidence of 24 per cent in a series operated on during the period from 1913 to 1923. Jackson (*Goiter and Other Diseases of the Thyroid Gland*, New York, Paul B. Hoeber, Inc., 1926, p. 242) said that the incidence of recurrences in his cases before the days of medication with iodine was 2 per cent. None of these writers, however, specifies the type of operation.

13. Jordan, S. M.: Basal Metabolic Rates and Their Relation to End-Results in Thyroid Disease: A Statistical Study, *Arch. Surg.* **11**:1 (July) 1925.

14. Smith, L. W.; Clute, H. M., and Strieder, J. W.: The Results in One Hundred Consecutive Cases of Hyperthyroidism Operated Upon, *Surg. Gynec. Obst.* **46**:325, 1928.

15. Kessel, L., and Hyman, H. T.: Exophthalmic Goiter and the Involuntary Nervous System: XVI. The Influence of Subtotal Thyroidectomy with and without Compound Solution of Iodine on the Course of the Disease, *Arch. Int. Med.* **40**:623 (Nov.) 1927.

16. Mason, J. T.: Mistakes in One Hundred Thyroidectomies, with Description of a New Method of Thyroid Cauterization in Treating Exophthalmic Goiter, *J. A. M. A.* **75**:160 (July 17) 1920.

17. Waits, C. E.: Preoperative and Postoperative Studies in Goiter, *J. M. A. Georgia* **11**:355, 1922.

18. Brodersen, N. H., and Harbitz, H. F.: Morbus Basedowii und Ergebnis seiner operativen Behandlung im Krankenhaus in Drammer, *Acta chir. Scandinav.* **61**:107, 1927.

19. Ladwig, A.: Nachuntersuchungen an Basedow-Operierten. Ein Beitrag zum Basedow-Problem, *Arch. f. klin. Chir.* **137**:367, 1925.

well, in 23 it was three months after the operation, in 21 within six months and in 14 after from one to three years. Only 4 patients in the whole series were considered to have thyrotoxicosis. Richter,⁷ of Chicago, in 1927 reported the results of "thyroidectomy" (evidently subtotal) in 100 cases of toxic goiter, of which 76 were of the exophthalmic type. The duration of the follow-up was not given. In 6 cases there was a persistently high rate of basal metabolism after operation and a second thyroidectomy was required. The same author more recently⁹ reported only "one definite failure to secure normal metabolism in 447 consecutive patients that were available for study." Frazier and Mosser,¹⁰ of Philadelphia, in 1928, reported a series of 100 cases of exophthalmic goiter "thoroughly followed" on a five-year plan in which a physical examination was attempted four times the first year, twice the second year and once yearly thereafter. Some patients who lived far away reported by letter. The thyroidectomy was usually subtotal. Several basal metabolic rates were determined but not reported. On the basis of an average postoperative interval of ten months, they said that 71 per cent of the patients were entirely well, 19 per cent had residual nervous symptoms but no hyperthyroidism, 6 per cent had "visceral changes" but no hyperthyroidism, 1 per cent had "persistent hyperthyroidism" unrelieved by operation and 4 per cent had "recurrent hyperthyroidism." While Pemberton¹¹ recently estimated the incidence of postoperative thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter at the Mayo Clinic as "certainly not more than 5 per cent," he realized that "the accuracy of any estimate of incidence would depend chiefly on the thoroughness and number of examinations and the interval elapsing since the operation."¹² Jordan,¹³ in 1925, at the

9. Richter, H. M.: Thyroidectomy, *Surg. Gynec. Obst.* **49**:67, 1929.

10. Frazier, C. H., and Mosser, W. B.: End-Results from the Surgical Treatment of Hyperthyroidism, *J. A. M. A.* **90**:657 (March 3) 1928.

11. Pemberton, J. deJ.: Recurring Exophthalmic Goiter: Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, *J. A. M. A.* **94**:1483 (May 10) 1930.

12. The statistics of Judd (Results of Operations for Adenoma with Hyperthyroidism and Exophthalmic Goiter, *Ann. Surg.* **72**:145, 1920) and of Pemberton (The End-Results of Surgery of the Thyroid Gland, *Arch. Surg.* **7**:37 [July] 1923) from the Mayo Clinic, based on a follow-up by letter of patients operated on in 1914 and 1916, respectively, and giving figures of 5.6 per cent and 11 per cent, respectively, for the incidence of postoperative thyrotoxicosis, are not directly pertinent here, as the type of operation varied greatly. Pemberton made statements regarding the interval histories of the patients, which suggest that the incidence a shorter time after operation may have been higher than 11 per cent. Mayo, in Keen's "Surgery" (Philadelphia, W. B. Saunders Company, 1921, vol. 8, p. 25), in speaking of the results of thyroidectomy, said that "in at least 10 per cent of simple and hyperplastic goiters operated on, there is some degree of recurrence." Ochsner, of Chicago (End-Results of Goiter Operations, *Ann. Surg.* **80**:388,

Clute.²¹ Of their 24 cases of thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter, there were persistences in 19 and recurrences in 5. In the recurrent cases there were no symptoms for an average of two years after operation, but in one case they were absent for only a few months. Richter⁷ remarked on the slight incidence of true recurrences. This scarcity of recurrences enables us to make the general statement that if after subtotal thyroidectomy for exophthalmic goiter the basal metabolism drops to normal and remains there when iodine is not being administered, for as long as two months,²² a cure can almost be assured.

It is also of prognostic interest that a basal metabolic rate of plus 15 per cent or higher during the administration of iodine for from ten to fourteen days after operation, usually means that the disease has not been abolished. On the other hand, if the basal metabolism is normal for from ten to fourteen days after operation and iodine is being administered, a cure can by no means be assured. While the data are not extensive enough for one to draw definite conclusions, it appears that similar prognoses may be made regarding patients who do not receive iodine during the immediate preoperative and postoperative periods. However, if the basal metabolic rate is normal for from ten to fourteen days after operation in these patients it can usually be assumed that the disease has disappeared. Segall and Means,²³ and Richardson and Means²⁴ observed that in cases in which the patients were apparently cured by subtotal thyroidectomy before the days of the use of iodine the basal metabolism was usually normal within two weeks after operation.

CHRONICITY

The chronicity of postoperative thyrotoxicosis is of interest. Good examples of this are given in charts 5, 8 and 9. In the cases of persistence in which measurement was possible, the shortest duration of the disease in a patient who received no other treatment after operation except iodine was one and one-fourth years. In two thirds of the

21. Lahey, F. H., and Clute, H. M.: Persistent and Recurrent Hyperthyroidism, *Ann. Surg.* **83**:199, 1926.

22. This figure is made to err on the side of conservatism, in order to allow ample time for the effect of medication with iodine to wear off. An interval of one month would be sufficient for practically all cases.

23. Segall, H. N., and Means, J. H.: The Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter, *Arch. Surg.* **8**:176 (July) 1924.

24. Richardson, E. P., and Means, J. H.: Results of Surgery and of Surgery Combined with Roentgen Ray Treatment in Exophthalmic Goiter, *Arch. Surg.* **2**:237 (Sept.) 1924. Means, J. H., and Richardson, E. P.: Diseases of the Thyroid, *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 1929, vol. 4, p. 208.

and poor in 8 (nearly 25 per cent), from one to thirteen years after subtotal thyroidectomy. Porter,² at the Massachusetts General Hospital in 1923, observed the basal metabolic rates in 28 of his 50 patients with toxic goiter on whom he had performed a subtotal thyroidectomy during the period between 1904 and 1921. In none was the basal metabolism above plus 10 per cent. It is to be noted, however, that some of these determinations of basal metabolism were made so long after operation that cases of temporary postoperative thyrotoxicosis may not have been detected. Thus Richardson,²⁰ also of the Massachusetts General Hospital, in 1923, in a one and one-half year follow-up which included physical examinations and determinations of the basal metabolism in 30 patients who had undergone subtotal thyroidectomy for exophthalmic goiter reported 5 cases (17 per cent) with postoperative thyrotoxicosis.

Thus it may be seen that the incidence of thyrotoxicosis after subtotal thyroidectomy for exophthalmic goiter, as given in the literature, ranges from about 0.25 to 25 per cent, many of the estimates falling in the vicinity of from 5 to 7 per cent. Our average of 19 per cent may appear high and give the impression that the end-results at the Massachusetts General Hospital have not been so good as those obtained elsewhere, owing perhaps to inadequate surgical measures. We are convinced that this does necessarily follow. From personal observation, we know that in some of the clinics from which the lower percentages have been reported the routine operation has been considerably less extensive than that carried out by the surgeons who have performed the most thyroidectomies at the Massachusetts General Hospital. The difference in incidence may be attributed in part to the manner in which the patients were followed. So far as clinical symptoms are concerned, our 37 postoperative toxic cases could be listed as follows: much improvement in 26 cases (70 per cent), moderate improvement in 10 cases (27 per cent) and no improvement in 1 case (3 per cent).

SCARCITY OF TRUE RECURRENCES

One outstanding feature of our study was the small number of recurrences, that is, cases in which the disease disappeared after operation and then recurred. In striking contrast to this conclusion was that of Pemberton¹¹ that most cases of postoperative thyrotoxicosis are recurrences and only a small number persistences. It is possible that this difference between the two conclusions may be attributed in part to the fact that Pemberton was unable to make frequent observations on his patients during the interval between the first and second operations. The marked predominance of persistences has been observed by Lahey and

20. Richardson, E. P.: Relative Value of Surgery and Roentgen Ray in Treatment of Hyperthyroidism, *J. A. M. A.* **80**:820 (March 24) 1923.

smallest percentage of persistences; by the fact that the thyrotoxicosis represented primarily a persistence of the disease rather than a recurrence, and by the fact that there was no outstanding difference before operation between the patients who were thyrotoxic following operation and those who were not. It may have been because operation was performed by the less experienced surgeons in a much larger percentage of cases in 1928 than in preceding years that the incidence was so high in that year. Else²⁷ reported that he has observed a considerable increase in the number of "recurrences" since "unspecialized general surgeons" have been doing goiter operations. Levin²⁸ was under the impression that "recurrences" are more common in goitrous areas, in which presumably lack of iodine is a factor.

The cause of true recurrences is not so easily explained. Just as the cause of the initial appearance of the disease is unknown so is it at present unknown why the condition should again become active after a period of quiescence. Pemberton¹¹ stated the belief that infections, overwork, worry, fright, shock, pregnancy and operations are important factors in recurrences. As stated previously, postoperative thyrotoxicosis, in general, seemed to be associated with the presence of a considerable amount of palpable thyroid tissue, and the amount was usually large in those patients who showed only temporary improvement during the administration of iodine. In the cases in which the disease finally disappeared and in which data were available (in case 1812, chart 3; in case 3913, chart 4, and in cases 2031, 2759 and 3961), the palpable tissue decreased markedly, usually to the point of becoming nonpalpable. Thus there was a rough parallelism between the amount of palpable tissue and the degree of thyrotoxicosis. It is of some diagnostic interest that, following subtotal thyroidectomy, an amount of thyroid tissue sufficient to be palpated with ease usually means that thyrotoxicosis is present. There are, of course, cases of severe postoperative thyrotoxicosis occasionally encountered in which no thyroid tissue can be palpated. Phemister²⁹ had a patient in whom two nodules, which at operation were only the size of a pea, were causing a severe persistence with a rate of basal metabolism of plus 50 per cent. Lahey and Clute,²¹ however, remarked that they had repeatedly been surprised at the size of the remnant at operation when none could be palpated beforehand, probably because it was situated on the posterior lateral aspects of the trachea.

27. Else (footnote 26, first reference).

28. Levin, S.: Comparative Study of 100 Subtotal Thyroidectomies from a Single Goiter Zone, *J. Michigan M. Soc.* **24**:527, 1925.

29. Phemister, in Miller, J. L.: Thyrotoxicosis from the Internist's Standpoint, *Am. J. M. Sc.* **177**:98, 1929.

cases of persistence the disease lasted for at least a year; in one quarter of the cases it persisted for at least from two to six years, without indication that it was coming to an end. Incidentally, one patient who was first operated on for exophthalmic goiter in the Massachusetts General Hospital in 1909 still had the disease in moderately severe form in 1927 in spite of two more thyroidectomies; that is, in this case there was a persistence of at least nineteen years. In one of the cases of recurrence in this series (chart 3), the thyrotoxicosis lasted a minimum of one year and possibly for from three to four years. We had great difficulty in finding a case in which the disease ended after a few months. The case of one patient in whom it apparently did so is not included in this study, because we were somewhat uncertain as to whether or not she was thyrotoxic after operation. The gain in weight and the diminution in nervousness, however, when the basal metabolic rate of this patient dropped to normal seven months after operation make it appear probable that she had thyrotoxicosis during the immediate post-operative period. Clute²⁵ gave the duration of persistences at the Lahey Clinic as from three months to fourteen years. It would be of interest to know what effect, if any, subtotal thyroidectomy has on the duration of the disease in these cases.

Not only was postoperative thyrotoxicosis a chronic condition in our cases of persistence, but it rapidly reached a steady state, and remissions were not noted, except those associated with the administration of iodine or the ending of the disease, and relapses were not observed, except those associated with the omission of iodine. This, together with the scarcity of true recurrences, leads us to wonder whether the remissions and relapses in the disease are not overemphasized. Either this is true, or else the thyrotoxicosis is different in this respect after operation than before.

CAUSE, INCLUDING RELATION TO EXTENT OF THYROIDECTOMY

Several observers²⁶ agreed that one of the chief causes of thyrotoxicosis following subtotal thyroidectomy is the removal of too little thyroid tissue. In our series, this idea is supported by the fact that the surgeons who did the most complete thyroidectomies had definitely the

25. Clute, H. M.: Hyperthyroidism Persisting after Thyroidectomy: The Necessity for Postoperative Examinations in Toxic Goiters, *S. Clin. North America* **6**:691, 1926.

26. Else, J. E.: Prevention of Recurrent Goiter, *S. Clin. North America* **8**:1375, 1928. Gilman, P. K., and Kay, W. E.: Certain Advantages of Total Thyroidectomy in Selected Cases of Thyrotoxicosis of the Exophthalmic Type, *Am. J. M. Sc.* **175**:350, 1928. Lahey, F. H.: Review of Another Year's Work with Thyroid Disease, *Boston M. & S. J.* **190**:153, 1924. Elliott (footnote 8). Frazier and Mosser (footnote 10). Smith, Clute and Strieder (footnote 14). Waits (footnote 17). Clute (footnote 25).

In such patients the disease must differ in some fundamental respect from that in the large number of cases in which it apparently comes to an end following one extensive thyroidectomy. If the reason for the new growth of thyroid tissue is merely that the cause of the disease is still active, it is remarkable that in at least 80 per cent of the cases of exophthalmic goiter the condition appears to be permanently cured by one subtotal thyroidectomy. It is difficult to understand why the cause of the disease should apparently suddenly cease to act altogether in such a large proportion of cases. The result one would expect would be a persistence of the disease in a mild form, according to the proportion of the gland left in situ. It is possible, of course, that the gland, having already shown marked hyperplasia, is unable to respond thus still further to any but strong stimuli. In this connection it is of interest that all of the cases like the three already mentioned, in which the disease showed such a striking tendency to persist, were in patients who originally had the disease in severe form, and in whom the accompanying emotional instability was marked. Certainly some powerful stimulus must be stimulating the thyroid in such a patient as in case 5581 (chart 7) in order to cause the lobe left in situ to double in size and the remnant on the hemithyroidectomized side to show marked proliferation.

The regrowth of thyroid tissue, although it may be marked, rarely reaches the size of the gland before surgical measures are used. This is probably the reason that the patients, although toxic, show improvement—there is merely a smaller mass of tissue to secrete the toxic agent, which is thus presumably secreted in smaller amount.

THE RESPONSE TO IODINE

On the whole, the response to iodine was much more satisfactory in this group than in an unselected group of patients with exophthalmic goiter who had not been otherwise treated. As previously demonstrated, in many cases the basal metabolic rate could be held at a constant level and the symptoms of thyrotoxicosis more or less completely controlled as long as iodine was continuously administered. These good results with iodine are possibly to be attributed to the decrease in the severity of the disease caused by operation, for, as we have shown,³⁰ there is a group of mild cases in which it is possible to treat the patients satisfactorily by iodine alone, whereas moderately severe and severe cases rarely show more than temporary improvement. It seems that similarly many of these cases of postoperative thyrotoxicosis can be carried along

30. Thompson, W. O.; Thompson, P. K.; Brailey, A. G., and Cohen, A. C.: Prolonged Treatment of Exophthalmic Goiter by Iodine Alone, *Arch. Int. Med.* 45:481 (April) 1930.

Persistence in Spite of Extensive Thyroidectomy.—In several instances in our series, even in cases of persistence, it was observed that the tissue palpable was not simply that left at operation, but was at least in part a new growth. Because of the marked propensity of the thyroid remnant to regenerate in some cases, it is probably impossible at present to prevent a certain amount of postoperative thyrotoxicosis, no matter how complete the thyroidectomy and by whom it is performed. This is illustrated by certain cases in the present study.

CASE 5581.—Miss V. G. (chart 7) had a right hemithyroidectomy for exophthalmic goiter March 16, 1928, about seven eighths of the lobe being removed. The administration of a compound solution of iodine was continued after operation, and by May 16, the basal metabolic rate was higher than it was during the administration of iodine just before operation; and not only were the left lobe and isthmus of the thyroid much larger, but there was also palpable tissue in the right lobe equal to at least three or four times the amount left at operation. On June 1, a second operation was performed, at which the isthmus and all except about 4 Gm. of the left lobe were removed. Following the operation the metabolism remained slightly elevated in spite of the administration of iodine, and by October 17, a mass of tissue the size of a walnut was palpable in the right lobe, and one the size of a cherry in the left lobe. About a month later the palpable tissue had increased still further in size. Omission of iodine on Feb. 25, 1929, was followed within a month by a rise in basal metabolic rate from plus 15 per cent to plus 38 per cent, and a return of all the signs and symptoms of thyrotoxicosis.

CASE 1915.—Mr. F. H. L., in whose case the data are recorded in chart 5, was apparently continuously thyrotoxic for a period of from twelve to sixteen years, in spite of two hemithyroidectomies and a subsequent subtotal thyroidectomy done by one of the two surgeons who do the most complete thyroidectomies and have the smallest incidence of postoperative thyrotoxicosis. The rate of basal metabolism at the time of the last observation was only slightly lower than before the first operation. Although recurrent tissue in the isthmus and in both lobes was removed in the subtotal thyroidectomy, there was a nodule in the left lobe of at least the size of a cherry at the time of the last observation.

CASE 6397.—The situation was somewhat similar in the case of Miss K. M. R., the data in whose case are given in chart 10. The thyrotoxicosis which had been present for about four years before admission to the hospital, and in which nervousness was perhaps the most outstanding feature, was only partially relieved by two subtotal thyroidectomies, although tetany followed the second. Within seven weeks after the first operation the basal metabolism was as high as it had been initially, and three weeks later, when induration had disappeared from the scar, a mass of thyroid tissue the size of a walnut was palpable on each side of the trachea. In another month and a half, this mass had doubled in size. There appeared to be a considerable amount of thyroid tissue palpable following the second operation, but there was still too much induration about the scar for us to be sure of this. (The short periods of normal metabolism following the operations during the administration of iodine probably do not represent true disappearances of the disease, but merely marked reductions in its intensity until thyroid tissue had time to regenerate.)

was not diseased, similar cardiac symptoms would rarely result from the same degree of thyrotoxicosis. Nevertheless, it seems reasonable to suppose that the extra load thus thrown on the heart probably causes some damage which, although not obvious at the moment, may show up in the course of time.

Else³⁴ and Levin²⁸ claimed that the postoperative administration of iodine prevents the regrowth of thyroid tissue after subtotal thyroidectomy for exophthalmic goiter; and Richter⁷ that it at least tends to lessen the number of recurrences. Marine and Lenhart³⁵ showed that the administration of iodine will prevent compensatory hyperplasia following partial removal of the thyroid in normal animals or in those with colloid goiter. This is a different matter, however, from preventing hyperplasia in the gland in exophthalmic goiter. On the other hand, Miller,³⁶ Clute²⁵ and Sloan³⁷ claimed that the postoperative administration of iodine does not prevent the regeneration of tissue or recurrence in exophthalmic goiter glands after thyroidectomy. Our observations appear to support this hypothesis. In other words, iodine does not seem to affect the cause of the disease. It follows that from the standpoint of prevention of postoperative thyrotoxicosis it is immaterial for how long the administration of iodine is continued after operation.

RELATION OF EXTENT OF THYROIDECTOMY TO MYXEDEMA, TETANY AND PARALYSIS OF THE RECURRENT LARYNGEAL NERVE

The large percentage of persistences in our series may not be an unmixed evil. We (W. O. T. and P. K. T.)³⁸ showed that true postoperative myxedema (not merely low basal metabolism) is at present a comparatively rare phenomenon at the Massachusetts General Hospital (about 1 per cent of the cases in which operation was done). Richardson³⁹ believed that "the removal of too much thyroid tissue is very improbable if the operation is carried out with due regard for the safety of the parathyroid glands and recurrent nerves." In certain other

34. Else, J. E.: Regeneration of the Thyroid Gland and the Prevention of Recurrent Goiters, *J. A. M. A.* **89**:2153 (Dec. 24) 1927.

35. Marine, D., and Lenhart, C. H.: Relation of Iodine to the Structure of Human Thyroids: Relation of Iodine and Histologic Structure to Diseases in General; to Exophthalmic Goiter; to Cretinism and Myxedema, *Arch. Int. Med.* **4**:440 (Nov.) 1909.

36. Miller, J. L.: Thyrotoxicosis from the Internist's Standpoint, *Am. J. M. Sc.* **177**:98, 1929.

37. Sloan, H. G., in discussion of article by Else (footnote 34).

38. Thompson, W. O., and Thompson, P. K.: Temporary and Permanent Myxedema Following Treated and Untreated Thyrotoxicosis, *J. Clin. Investigation* **6**:347, 1928.

39. Richardson, E. P.: Personal communication to the authors.

for years on such a regimen and, at least in some instances, until the disease disappears (case 1812, chart 3; case 3913, chart 4, and case 2031). Read³¹ and Jackson³² reported satisfactory control of postoperative thyrotoxicosis by the use of iodine. At the Lahey Clinic, Smith, Clute and Strieder¹⁴ reported that of 7 cases of persistence only 2 were uncontrolled by iodine. In reports from the same clinic by Clute²⁵ and Lahey and Clute,²¹ however, it was stated that in several of the cases in which there was thyrotoxicosis following operation iodine was administered for a year or more, usually with temporary, but in no case permanent, improvement. In our series it was more common for the rate of basal metabolism to remain depressed at a more or less constant level as long as iodine was continuously administered, than for the depression to be only temporary. It is a matter of considerable interest that while the metabolism could be held at a fairly constant level by the administration of iodine in so many cases, there were only 6 cases in which it was constantly held below plus 10 per cent.

But for the use of iodine postoperatively, more of these patients would have come to second operation; incidentally this is a different matter from the number of patients having persistence of the disease. The fact that the basal metabolism can be held at a constant level by iodine, however, does not necessarily mean that the result is entirely satisfactory. The best results would probably be secured by reoperating in all cases in which the basal metabolism cannot be held indefinitely at plus 15 per cent or lower by the administration of iodine.³³ While in some patients in whom it is held at this or a slightly higher level the thyrotoxicosis is held fairly well in check, nevertheless a few signs and symptoms may be detected by careful observation. There is reason to suppose that the continued maintenance of a basal metabolic rate of from plus 15 to 25 per cent for several years may result in damage to the circulatory and other systems. For example, in a girl, aged 16 (lab. no. 5040, not in this series), the slight load imposed on a damaged heart (rheumatic) by mild postoperative thyrotoxicosis (with a metabolism of plus 25 to 30 per cent in spite of medication with iodine) caused symptoms of mild cardiac failure. When this load was removed by a second operation (subtotal) and the basal metabolism was restored to normal, these symptoms disappeared and the patient's heart was able to meet the demands of ordinary routine. In a patient whose heart

31. Read, J. M.: The Use of Iodine in Exophthalmic Goiter, *Endocrinology* 8:746, 1924.

32. Jackson, A. S.: *Goiter and Other Diseases of the Thyroid Gland*, New York, Paul B. Hoeber, Inc., 1926.

33. This will automatically include most patients with a large amount of palpable thyroid tissue. Treatment with roentgen rays is, on the whole, a rather unsatisfactory method.

Boothby⁴² were under the impression that postoperative tetany has increased since subtotal thyroidectomies have become more extensive. There were 3 patients with postoperative tetany among the 266 patients operated on during the six year period included in our study. Two cases occurred in patients who were not thyrotoxic after operation. One of these patients died shortly after operation. In the other, the signs and symptoms of tetany practically cleared up, although the concentration of calcium in the serum remained rather low. In the third patient, the tetany was still marked up to the time of writing. The first 2 patients were among those operated on by a surgeon who had one of the smallest number of persistences. The third patient (no. 6397, chart 10 in this study) was among those operated on by another surgeon who had a high percentage of persistences, which he was much interested in reducing. On this patient he performed two subtotal thyroidectomies, and at the second operation he made the removal of the remaining thyroid tissue much more thorough than was his usual practice. Nevertheless, he took care to identify and to leave two parathyroids, so that tetany was apparently an unfortunate coincidence.

Paralysis of the recurrent laryngeal nerve has not been common at this hospital and has usually been transient in its effect on phonation. It may occur following incomplete thyroidectomy.

In the hands of the average surgeon, more radical thyroidectomies would probably mean more tetany, more recurrent paralysis of the laryngeal nerve and more laryngeal edema. It is our impression, however, that there is about as little danger of these complications when an experienced surgeon does an extensive thyroidectomy as when an inexperienced one does a much less extensive operation.

SUMMARY

Of 190 cases of exophthalmic goiter in which the patients underwent subtotal thyroidectomy during the years 1923 to 1928 at the Massachusetts General Hospital and which were followed for from three months to nearly six years after operation with frequent physical examinations and tests of basal metabolism, 37, or 19.5 per cent, showed definite clinical evidence of postoperative thyrotoxicosis with basal metabolic rates ranging from plus 19 to plus 63 per cent without medication.

In only 2 instances was there evidence that it was a true recurrence rather than a persistence of the disease. In 3 cases, however, regeneration of thyroid tissue was observed in association with a persistence. This condition was sometimes noted in spite of the administration of iodine and repeated subtotal thyroidectomies.

42. Boothby, W. M., in discussion of article by Elliott (footnote 41).

clinics, however, the incidence of myxedema is said to have increased as the thyroidectomies have become more extensive. For example, according to Richter,⁹ thyroidectomies sufficiently extensive to cause a high percentage of cures "will result in a high incidence of temporary hypothyroidism." Gilman and Kay²⁶ reported that 19 of 20 patients who underwent a so-called total thyroidectomy required the administration of desiccated thyroid following operation (the other patient died), but the reasons for assuming that an underfunction of the thyroid was present were not stated in most instances. In 2 other patients in their series who required no desiccated thyroid following operation, a nodule of tissue 1 by 1 cm. was left in by request. Smith, Clute and Strieder¹⁴ said that the incidence of postoperative myxedema has increased in the last three years at the Lahey Clinic, in association with a marked increase in the amount of tissue removed at operation and the use of iodine postoperatively. Richter,⁹ indeed, regarded hypothyroidism as the goal of subtotal thyroidectomy. We are not convinced that an underfunction of this important organ is any more desirable than a mild overfunction.

Of course, care must be taken to distinguish between a low rate of basal metabolism caused by an underfunction of the thyroid and one associated with other conditions.⁴⁰ If it be true, however, that extensive thyroidectomies result in a high incidence of myxedema, then in our opinion the goal of surgery is to leave in an amount of tissue large enough to prevent the development of myxedema and small enough to prevent a persistence of the disease. Much can undoubtedly be done in this direction, but the goal will be hard to achieve because of the variation among patients in the amount of this tissue and the technical difficulties of leaving in only a certain amount at operation. These obstacles perhaps serve to emphasize that surgical intervention, while at present the best method of treatment for exophthalmic goiter, is in reality a rather crude one.

The incidence of tetany, at present a much more serious sequel than the persistence of exophthalmic goiter in a mild form, is low, being only about 1 per cent. Figures showing the incidence of tetany following operations for goiter at other clinics are not available. Elliott⁴¹ and

40. Thompson, W. O.; Thompson, P. K., et al.: Low Basal Metabolism Following Thyrotoxicosis: I. Temporary Type without Myxedema, with Special Reference to the Rôle of Iodine Therapy, *J. Clin. Investigation* 5:441, 1928; Low Basal Metabolism Following Thyrotoxicosis: II. Permanent Type without Myxedema, *ibid.* 5:471, 1928; Significance of Low Basal Metabolism Following Thyrotoxicosis, *Am. J. Surg.* 7:48, 1929. Thurmon, F. M., and Thompson, W. O.: Low Basal Metabolism without Myxedema, *Arch. Int. Med.* 46:879 (Nov.) 1930.

41. Elliott, C. A.: Results of Thyroidectomy for Hyperthyroidism as Indicated by Examination a Year or More Following Operation, *Tr. A. Am. Physicians* 41:93, 1926.

If the basal metabolism is plus 15 per cent or higher for from ten to fourteen days after a subtotal thyroidectomy for exophthalmic goiter and if the patient is receiving iodine during this period, it is probable that the disease will persist. On the other hand, a normal metabolic rate under these conditions does not mean that the disease has been abolished.

If, following subtotal thyroidectomy, a patient has a normal metabolism for as long as two months during a period in which he is not receiving iodine, the danger of his having the disease again is slight.

Thyrotoxicosis is almost always present if following subtotal thyroidectomy for exophthalmic goiter there is an amount of thyroid tissue sufficient to be easily palpable.

It is probably desirable to reoperate on all patients in whom the basal metabolic rate cannot be held at or near the standard normal level by the continuous administration of iodine until the disease disappears.

The favorable response to prolonged medication with iodine noted in many patients after subtotal thyroidectomy is similar to the favorable response noted in many patients who have the disease in mild form but who have not been otherwise treated, and may be the result of reduction in the severity of the disease following operation.

The postoperative administration of iodine does not prevent the regeneration of thyroid tissue or a persistence of thyrotoxicosis.

The marked chronicity of the thyrotoxicosis following subtotal thyroidectomy suggests that in such instances the disease may last as long as it would have if no operation had been performed.

The postoperative thyrotoxicosis lasted from about two to four years in the 3 cases in which it finally disappeared without further surgical measures or roentgen treatment. It lasted for at least one year in 19 others and at least from four to six years in 4 others.

The degree of thyrotoxicosis was usually not severe; with a single exception, it was less than before operation. All of the patients resumed their customary occupation, although under a definite handicap in the instances in which the disease persisted in moderately severe and in severe form.

In 18 cases the basal metabolism could be held at a constant level for from months to years by the prolonged administration of iodine. In 10 cases in which iodine was ineffective, or eventually became so, or in which it did not abolish the thyrotoxicosis completely enough, reoperation was recommended. In 7 cases roentgen therapy was tried, with fair results in 5 instances.

From a preoperative standpoint, there was no definite distinguishing mark between those patients who had thyrotoxicosis following operation and those who did not.

There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of thyrotoxicosis.

The surgeons who did the most radical thyroidectomies (synonymous in general with those who had the most experience) had definitely a smaller percentage of cases of postoperative thyrotoxicosis than did the surgeons who had less experience and who usually did less extensive thyroidectomies.

In the cases of persistence of the disease, we noted no relapses except those caused by the omission of iodine, and no remissions except those caused by its administration and the disappearance of the disease.

CONCLUSIONS

Thyrotoxicosis following a subtotal thyroidectomy for exophthalmic goiter appears in most cases to be caused by the removal of too little thyroid tissue at the time of operation.

A reduction in the incidence of postoperative thyrotoxicosis without an increase in the incidence of myxedema, tetany or paralysis of the recurrent laryngeal nerve, however, will occur only when more radical thyroidectomies are performed by surgeons specially trained to do this type of work.

Owing to the marked propensity of the remnant of thyroid tissue to regenerate shortly after operation in some cases, it is probably impossible at present to prevent a certain amount of persistence of the disease no matter how complete the thyroidectomy (exclusive of complete extirpation) and by whom it is performed.

determined by the type of disease present. They were impressed with the fact that a single and, occasionally, a repeated Rehfuß fractional test meal is not enough to establish the diagnosis of true achlorhydria or achylia gastrica. In the group of false diagnoses of achylia a small amount of acid is produced and is neutralized by duodenal regurgitation or perhaps by the protein from a gastric carcinoma or other neoplasm that is breaking down. Winkelstein and Marcus stated that they did not encounter one case of pernicious anemia in which neutral red was excreted.

METHOD OF DETECTION OF NEUTRAL RED IN EXTRACTED SPECIMENS

A Rehfuß tube is introduced into the "fasting stomach," and the stomach is washed with water until the contents return water clear. Two cubic centimeters of a 2 per cent solution of neutral red (40 mg.) is injected intramuscularly into the gluteal region. The stomach is then aspirated every fifteen minutes for two hours. Each specimen is kept in a separate test tube. In cases in which there is very little or no gastric secretion, a quantity of water, 15 or 20 cc., is introduced into the stomach through the tube and aspirated at the end of the fifteen minute periods.

The gastric contents are then treated in the following manner: To 15 or 20 cc. of the contents of the stomach, approximately 2 Gm. of tribasic lead acetate is added, and the tube shaken. If the contents seem to contain a large quantity of bile, about 1 Gm. of purified animal charcoal is also added. This is filtered through filter paper, and within a few minutes sufficient filtrate is obtained to fill a small test tube. When smaller quantities of the contents of the stomach are used, proportionate amounts of the lead acetate and charcoal are employed. A few drops of glacial acetic acid are added to the filtrate while it is viewed against a pure white background (such as white paper) and while a control tube with plain water is held next to it. When neutral red is present the solution will begin to assume a pinkish color within a few seconds. The depth of the color is proportional to the concentration of the dye. We have not attempted to determine the quantitative output of the neutral red.

REPORT OF CASES

CASE 1.—C. B., a woman, aged 38 years, six weeks prior to admission to the hospital began to complain of increasing weakness, discoloration of the skin and a tingling sensation in the fingers. The patient showed an icteric tint to conjunctiva, marked atrophic glossitis, a hard spleen, the absence of knee jerks, diminished deep reflexes, blurred disks and retinal hemorrhages.

The results of a roentgen examination of the gastro-intestinal tract were negative. The gastric extraction on admission to the hospital showed: free acidity, 0 0 0 0 0 0; total acidity, 5 0 10 12 10 5. The guaiac reaction was negative. Gastric extraction two weeks later showed: free acidity, 0 0 0 0 0 0; and total acidity, 10 12 38 50 20 10. The guaiac reaction and the test for lactic acid were negative. The blood count on admission showed: red blood cells, 1,596,000 per cmm.; white blood cells, 2,400 per cmm., and hemoglobin (Dare), 28 per cent. The color index was 0.9. The differential count showed: polymorphonuclears,

THE NEUTRAL RED TEST IN PERNICIOUS ANEMIA *

S. J. COHEN, M.D.

M. J. MATZNER, CH.E., M.D.

AND

IRVING GRAY, M.D.

BROOKLYN

During the past year we were able to demonstrate the presence of injected neutral red in the gastric extractions of three patients who had pernicious anemia. These determinations prompted us to make this report.

The use of neutral red has been advocated in the study of the gastric secretory function. Fuld¹ discovered that neutral red would appear in a Pavlov pouch after the dye was placed in the large stomach. Several years later, Finkelstein² found that it was practically the only dyestuff eliminated in appreciable quantities in the Pavlov pouches of dogs after intramuscular administration. One year later, Glaessner and Wittgenstein³ applied this fact clinically.

Davidson, Willcox and Haagensen⁴ concluded that neutral red was excreted in achylia accompanying every condition except pernicious anemia. In their studies, they investigated eight cases of pernicious anemia, and did not recover neutral red in the gastric extractions after two hours. Their statement that the absence of the dye in pernicious anemia, in contrast to its excretion even in small amounts in carcinoma with anacidity, and secondary anemia with anacidity, is of definite practical value.

In a recent communication, Winkelstein and Marcus⁵ stated that true achlorhydria occurs in a variety of conditions, and that the failure of neutral red to appear is linked with the absence of the acid and is not

* Submitted for publication, April 21, 1930.

* From the medical service of Dr. Meyer Rabinowitz, Gastro-Intestinal service of Dr. Irving Gray and the Department of Pathology, Jewish Hospital of Brooklyn.

1. Fuld, E.: München. med. Wchnschr. **43**:908, 1908.

2. Finkelstein, R.: Arch. f. Verdauungskr. **30**:299, 1923.

3. Glaessner, K., and Wittgenstein, H.: Klin. Wchnschr. **2**:1650 (Aug. 27) 1923.

4. Davidson, P. B.; Willcox, E., and Haagensen, C. D.: Gastric Excretion of Neutral Red, J. A. M. A. **85**:794 (Sept. 12) 1925.

5. Winkelstein, A., and Marcus, J.: Excretion of Neutral Red in the Stomach in Achylia Gastrica, J. A. M. A. **92**:1238 (April 13) 1929.

Examination showed marked pallor, atrophy of the marginal papillae of the tongue, presence of the knee jerks, the loss of vibratory sensation and a diminished tactile sensation in the lower extremities. The Babinski sign was present on the patient's right side. The results of the roentgen examination of the gastrointestinal tract were negative. Repeated gastric analyses showed no free hydrochloric acid (one study was made with histamine as the gastric stimulant).

The blood count showed: red blood cells, 2,140,000; white blood cells, 3,800, and hemoglobin (Dare), 50 per cent. The color index was 1.1. The differential count showed: platelets, 170,000; polymorphonuclear neutrophils, 63 per cent; polymorphonuclear eosinophils, 1 per cent, and small lymphocytes, 36 per cent.

Macrocytosis and polychromasia were moderate; microcytosis was slight. There was a reticulation of 0.5 per cent.

COMMENT

We are not able to state whether the neutral red recovered in the gastric extractions of these patients was actually secreted by the gastric glands or whether it was regurgitated from the duodenum into the stomach. Experimental work in herbivorous and omnivorous animals by Piersol, Bockus and Banks⁶ definitely showed that neutral red is excreted to a considerable degree in the bile as well as in the intestinal glands from the duodenum to the ileum. The possibility that the dye might be swept back into the stomach by duodenal regurgitation, particularly in cases of achylia in which the pylorus is frequently open, should receive serious consideration.

The presence or absence of bile in the extracted specimens, as shown by Medes and Wright,⁷ does not determine whether or not there has been duodenal regurgitation. They found in their studies evidences of duodenal regurgitation even in the absence of bile in the extracted specimens. In brief, these authors showed that bile is regurgitated rarely without trypsin, and that trypsin is regurgitated much more frequently without bile.

The possibility that the neutral red recovered in these cases was of gastric origin cannot be excluded. One cannot depend entirely on the appearance and color of the extracted specimen to determine whether or not neutral red is present. Bile pigment, if present, must be removed, and in any event the specimen must be acidified in order to establish definitely the presence or absence of the dye.

We are now engaged in the study of the biliary excretion of neutral red in man by injecting it at variable times prior to cholecystectomy.

SUMMARY

1. Three cases have been reported of patients with pernicious anemia in whom injected neutral red was recovered in the gastric extractions.

6. Piersol, G.; Bockus, H., and Banks, J.: *Am. J. M. Sc.* **170**:405, 1925.

7. Medes, G., and Wright, C. B.: *J. Clin. Investigation* **6**:403 (Dec.) 1929.

57 per cent; small lymphocytes, 38 per cent; eosinophils, 2 per cent; metamyelocytes, 2 per cent, and myelocytes, 1 per cent.

Anisocytosis and macrocytosis were moderate. There was marked poikilocytosis and slight polychromasia. The hemolysis test started at 0.42 per cent sodium chloride, and finished at 0.34 per cent.

CASE 2.—G. W., a woman, aged 28, had for five months complained of weakness, a sore tongue and increasing pallor. Examination showed a lemon yellow

TABLE 1.—*Results of Testing the Contents of the Stomach to Determine the Presence of Neutral Red*

Specimen	Acid	Dye	Time
1.....	0	0	15 min.
2.....	0	0	30 min.
3.....	0	0	45 min.
4.....	0	0	1 hr.
5.....	0	0	1¼ hr.
6.....	0	0	1½ hr.
7.....	0	Present	1¾ hr.
8.....	0	Present	2 hr.
Bilirubin: direct, negative; indirect, 2 units			
Icteric index, 15			

TABLE 2.—*Test for Neutral Red*

Specimen	Free Acid	Total Acidity	Dye	Time
1.....	0	6	0	30 min.
2.....	0	8	0	45 min.
3.....	0	6	Present	1 hr.
4.....	0	10	Present	1½ hr.
5.....	0	6	0	2 hr.

TABLE 3.—*Test for Neutral Red*

Specimen	Free Acid	Dye	Time
1.....	0	0	20 min.
2.....	0	0	40 min.
3.....	0	Present	1 hr.
4.....	0	0	1½ hr.
5.....	0	Present	2 hr.

skin, atrophic glossitis and a palpable spleen. The results of a roentgen examination of the gastro-intestinal tract were negative. Gastric analysis, including a fractional study with histamine as the stimulant, made on four occasions, failed to disclose any free hydrochloric acid. The blood count was: red blood cells, 2,800,000 per cmm.; white blood cells, 6,600 per cmm.; hemoglobin (Dare), 45 per cent. The color index was 0.9. The differential count showed: polymorphonuclears, 42 per cent; lymphocytes, 56 per cent, and eosinophils, 2 per cent.

There was marked anisocytosis, macrocytosis, polychromasia and poikilocytosis, and slight microcytosis.

CASE 3.—M. W., a woman, aged 51 years, for the past few months had complained of numbness, weakness of the lower extremities and progressive anemia.

THE DIAGNOSTIC VALUE OF THE SUGAR TOLERANCE CURVE IN ENDOCRINOPATHIES *

B. Y. GLASSBERG, M.D.

ST. LOUIS

Since Hofmeister (1888) first reported mellituria in dogs following the administration of dextrose, and Jacobson (1913) proposed a series of blood sugar determinations, as tests offering certain aids in the diagnoses of diseased states, particularly the endocrinopathies, there has been a regrettable confusion in the prolific literature pertaining to the sugar tolerance test. The work of the earlier investigators in general may be disregarded, because the methods were inexact, and the results necessarily unreliable.

With certain minor variations, the test consists in the administration of a standard amount of dextrose (100 Gm.) and the estimation of the sugar in the blood and urine at intervals thereafter. The proponents of this test base their diagnostic interpretation on the height attained by the curve, the rapidity of its return toward normal and the level of the blood sugar three hours after the administration of dextrose as compared with its level at the beginning of the test.

In order to reevaluate this test, I have analyzed over 300 sugar tolerance curves made in the Jewish Hospital in the last three years. During this period the same technician continuously employed the same method for determining the blood sugar (Shaffer-Hartmann). The micro-technic requiring 0.2 cc. of capillary (arterial) blood, which is rapidly finding extensive favor, was used.

Of the curves analyzed, eighty-five were grouped according to the diagnosis in the following classification: "normal," hyperthyroid, hypothyroid, hypopituitary and a combination hypothyroid-hypopituitary type.

A glance at the chart, a graphic compilation of the observations in eighty-five cases, shows the lack of diagnostic significance that may be attached to the sugar tolerance curve because (*a*) the various cases of the same disease differ so widely in the blood sugar values, and (*b*) on the whole, the trend of the curves is not markedly different in the four conditions studied from that in the "normal" person.

Table 1 shows that the sugar tolerance curve repeated within a few days gives wide and inconstant variations.

* Submitted for publication, May 17, 1930.

* From the medical service of the Jewish Hospital, St. Louis.

2. Previous investigators have emphasized the diagnostic value of the neutral red test in pernicious anemia.

3. Investigators have never before been able to recover neutral red in the gastric specimens in true pernicious anemia.

4. The value of the test for neutral red is always questionable, because the presence of the dye in the stomach may be accounted for by regurgitation of the duodenal content.

5. A simple and rapid method for the detection of neutral red in the gastric content is described.

6. The presence of neutral red in the gastric extractions does not in itself exclude the diagnosis of pernicious anemia.

TABLE 1.—*Variations in the Blood Sugar Tolerance Curves in the Same Patient When Routine Tests Were Made Within a Few Days*

Case	Number of Test	Before Administration of Dextrose	After Administration of Dextrose								
			Mg. of True Sugar per 100 Ce. of Blood								
			½ Hour		1 Hour		2 Hours		3 Hours		
			Diff.	Diff.	Diff.	Diff.	Diff.	Diff.			
1	First.....	120		215		175		145		80	
	Second.....	115	+ 5	200	+15	180	— 5	160	—15	80	± 0
2	First.....	110		255		265		215		175	
	Second.....	70	+40	180	+75	200	+65	175	+40	145	+30
3	First.....	75		175		240		275		215	
	Second.....	100	—25	245	—70	325	—85	290	—15	160	+55
4	First.....	105		175		260		280		250	
	Second.....	100	+ 5	185	—10	250	+10	250	+30		
5	First.....	125		195		250		240		230	
	Second.....	125	± 0	200	— 5	195	+55	195	+45	195	—35
	Third.....	130	— 5	195	+ 5	205	—10	195	± 0	160	—35
Average deviation.....		13		30		40		24		26	

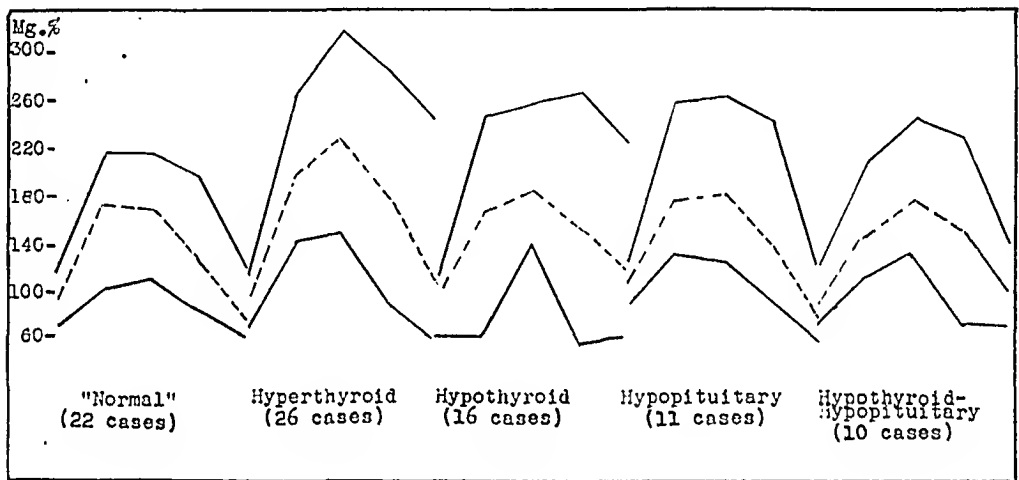
TABLE 2.—*Variations in the Blood Sugar Tolerance Curves of the Capillary Blood with and without the Administration of Water*

		Before Adminis- tration of Dextrose	After Administration of Dextrose									
			Mg. of True Sugar per 100 Ce. of Blood									
Case	Fluids		Diff.	½ Hour		1 Hour		2 Hours		3 Hours		
					Diff.		Diff.		Diff.		Diff.	
1	Without....	58		132		126		98		70		
	With.....	82	—24	126	+ 6	150	—24	116	—23	95	—25	
2	Without....	91		145		193		167		127		
	With.....	84	+ 7	142	+ 3	200	— 7	181	+36	106	+21	
3	Without....	79		217		195		149		54		
	With.....	84	— 5	176	+41	207	—12	121	+28	67	—13	
4	Without....	80		126		151		144		134		
	With.....	87	— 7	180	—54	218	—68	156	—12	84	+50	
Average deviation.....		11		26		28		25		27		

TABLE 3.—*Variations in the Blood Sugar Tolerance Curves of the Venous Blood with and without the Administration of Water*

		Before Adminis- tration of Dextrose		½ Hour		1 Hour		2 Hours		3 Hours	
		After Administration of Dextrose									
		Mg. of True Sugar per 100 Cc. of Blood									
Case	Fluids	Diff.		Diff.		Diff.		Diff.		Diff.	
1	Without....	66		72		75		69		65	
	With.....	79	—13	98	—26	107	—32	77	— 8	60	+ 5
2	Without....	89		142		182		135		117	
	With.....	84	+ 5	133	+ 9	174	+ 8	124	+11	78	+39
3	Without....	78		190		184		127		54	
	With.....	90	—12	160	+30	172	+12	97	+30	52	+ 2
4	Without....	76		107		142		139		118	
	With.....	77	— 1	171	—64	197	—55	154	—15	78	+40
Average deviation.....		8		32		27		16		22	

In order to study at least one of the factors involved in this variability, I performed a test on four "normal" patients, giving dry dextrose without any fluid, and repeated the test within two or three days, this time giving the same amount of dextrose with a considerable quantity of water (from 800 to 1,200 cc.) during the course of the examination. The sugar was determined in both capillary (arterial) and venous blood in triplicate, employing Somogyi's (1929) technic. In table 2 are recorded the observations on capillary blood. In the first case the curves are almost identical, except at the one-half hour period, if the difference found in the sugar content during fasting is subtracted from the difference found during the other periods in the examination. However, in the other cases there is a striking variability amounting in the third case at the half-hour period to 41 mg. per hun-



Graphic reconstruction of a table (omitted because of its unwieldiness) showing maximum (upper straight line), average (broken line) and minimum (lower straight line) levels of eighty-five classified sugar tolerance curves. Note that the overlapping of the curves is such as to preclude almost entirely any diagnostic significance of any one sugar tolerance test.

dred cubic centimeters and in the fourth case to 68 mg. per hundred cubic centimeters at the one hour period. The average deviation, it is true, is only about 15 mg. per hundred cubic centimeters if the deviation during the fasting period is subtracted from that found during the other periods. However, it is obvious that little diagnostic significance can be attached to the test when the mere variation in fluid intake causes as much as 68 mg. per hundred cubic centimeters difference in the sugar value.

In table 3 are recorded the differences in venous sugar content after the administration of dry dextrose and after the administration of the same quantity of dextrose with a considerable amount of water (from 800 to 1,200 cc.). Throughout this table there are rather striking differences

THE REFLEX INFLUENCE OF THE COLON, APPENDIX AND GALLBLADDER ON THE STOMACH*

FRED M. SMITH, M.D.

AND

GEORGE H. MILLER, M.D.

IOWA CITY

The present investigation was suggested by the study of the gastric manifestations associated with an irritable colon.¹ The epigastric distress was demonstrated to be gastric in origin. It is intensified by an aggravation of the bowel symptoms, and may be induced by a distention of the colon. In the roentgen examination of the gastro-intestinal tract, a pyloric spasm was the most prominent observation. There was also frequently an increase in the peristaltic action of the stomach. These observations were not constant and varied in different persons, but they were more evident during periods of apparent increased tension in the colon. These observations suggested that an alteration in the tone, particularly in the pyloric region and in the peristaltic action, was responsible for the epigastric distress, and that the latter was induced by a stimulation from the colon.

Clinical and roentgen observations² have strongly supported the theory of a reflex stimulation of the stomach from the gallbladder and the appendix. Experimental investigations of the problem have been concerned chiefly with the study of the reflex connection between the colon and the stomach.

* Submitted for publication, May 28, 1930.

* From the Department of Internal Medicine, State University of Iowa.

* Presented in part before the Society of Clinical Investigation at Atlantic City, May 6, 1929, and before the International Physiological Congress, Boston, Aug. 20, 1929.

1. Smith, Fred M.; Miller, G. H., and Fowler, W. M.: The Gastric Manifestations Associated with a Spastic Colon, *J. A. M. A.* **93**:1932 (Dec. 21) 1929.

2. Cole, L. G.: Physiology of the Pylorus, Pileus Ventriculi and Duodenum, as Observed Roentgenographically, *J. A. M. A.* **61**:762 (Sept. 6) 1913; Relation of Lesions of the Small Intestine to Disorders of the Stomach and Cap, as Observed Roentgenologically, *Am. J. M. Sc.* **148**:92, 1914. Brown, H. G.: Diagnosis of Certain "Stomach Cases," *South. M. J.* **7**:617, 1914. Aaron, C. D.: Chronic Appendicitis, Pylorospasm and Duodenal Ulcer, *J. A. M. A.* **64**:1845 (May 29) 1915. Finney, J. M. T., and Friedenwald, J.: Pylorospasm in Adults: Its Medical and Surgical Treatment, *Am. J. M. Sc.* **162**:469, 1921.

in the sugar content. As in the other instance, there is no uniform deviation in the form of the curve occasioned by the quantity of water taken during the test. The differences here amount to from 30 mg. more to 64 mg. less per hundred cubic centimeters at the half-hour period and even at the three hour period from 2 to 40 mg. more per hundred cubic centimeters in the second test.

CONCLUSIONS

1. After a statistical analysis of eighty-five sugar tolerance tests done as a routine in the Jewish Hospital of St. Louis on a series of normal and endocrinopathic patients, I am unable to find any one curve which may be considered diagnostic of any of the conditions under consideration.

2. Statistical analysis of curves repeated within a few days of the first routine sugar tolerance test shows no uniformity in the results, thus precluding further a diagnostic interpretation of the curve obtained.

3. Careful determination of the capillary (arterial) and venous blood sugar after the administration of a standard dextrose meal with and without the ingestion of water shows no uniform deviation in the form of the curve. Such a critical analysis did show that the intake of fluid alone produced a tremendous but not a constant deviation in the curve.

4. For the reasons presented here, I feel that the sugar tolerance curve as we have used it as a routine up to this time yields no information of diagnostic value in the differentiation of normal and endocrinopathic conditions.

Metropolitan Building.

Pearcy and Van Liere⁸ reported an immediate reduction in the tone of the stomach, cessation of contractions and an inhibition of the pyloric and cardiac sphincters of the dog following a distention of the esophagus, duodenum, jejunum or colon, by means of a balloon. They furthermore indicated that a distention of any portion of the gastrointestinal tract induced an inhibition of the remaining sections.

In the present investigation, the influence of the irritation of the colon, appendix and gallbladder by croton oil on the tone and peristaltic action of the stomach was studied. Dogs anesthetized with barbitol were employed. The stomach and the proximal part of the colon were exposed by a midline incision. The ileum was ligated or sectioned at its junction with the cecum in order to limit the action of the irritant to the colon. A balloon was introduced into the pyloric portion of the stomach through the duodenum, and the peristaltic action recorded on a

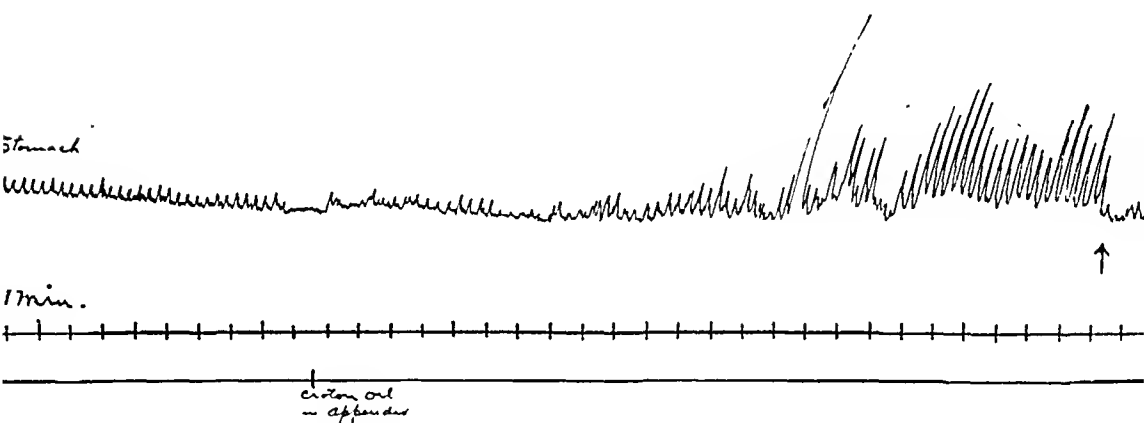


Chart 1.—Gastric activity after introducing croton oil into the first portion of the colon. It is noted that there was a striking increase in the peristaltic waves on distending the colon with air which subsided promptly on releasing the tension. The same characteristic response was again obtained which was later followed by an abrupt reduction in peristalsis subsequent to the administration of atropine.

kymograph. After a control period, a few drops of croton oil were introduced into the proximal colon by means of a syringe and small-bore needle. Within a few minutes there was usually an increase in tone and a marked increase in the peristaltic action of the stomach which frequently became violent; occasionally, reverse waves were observed. This increased tone and peristaltic action of the stomach was intensified by distending the colon (chart 1). The effect of increasing and decreasing the tension of the colon following the application of the irritant were striking. The peristaltic waves were at once intensified by

8. Percy, J. F., and Van Liere, E. J.: Studies on the Visceral Nervous System: 1. Reflexes to the Stomach, *Am. J. Physiol.* **78**:64, 1926.

Cannon³ observed a delay in the emptying time of the stomach following an irritation of the colon. This observation stimulated others to adopt a similar method in the investigation of the reflex connection between the colon and the stomach. White,⁴ in a correlated, clinical and experimental study, concluded that a delay in the emptying time of the stomach is an exception in lesions of the lower part of the bowel. In the experimental animals, the results of introducing a strong irritant into the cecum were variable. Intense irritation induced vomiting; a less intense irritant was followed either by a delay or an increase in the time in which the gastric contents were expelled, whereas moderate stimulation had no apparent effect. Monroe and Emory⁵ recently reported experiments in which the emptying time of the stomach of the dog was studied before and after the introduction of turpentine into the colon. They concluded that an irritation confined to the colon had no appreciable effect on the pyloric mechanism and the gastric peristalsis from the standpoint of the ability of the stomach to discharge its contents, and suggested that "so-called" gastric symptoms associated with colitis do not originate in the stomach.

Hughson⁶ was concerned primarily with the investigation of the relationship of the reflex pylorospasm to the diseases of the digestive organs, and studied the influence of the trauma incident to the various operative procedures on the abdominal viscera on the emptying time of the stomach. He noted that the traumatization of any abdominal viscus in the dog by surgical procedure prolonged the emptying time of the stomach approximately 67 per cent for a period of about two weeks, and that the speed of the contraction waves was increased. He advanced a hypothesis that a spasm of the pylorus resulting from disease either within or adjacent to the abdominal cavity is solely due to an irritation of the peritoneal surface.

Barber and Stewart⁷ noted striking changes in the peristaltic activity of the stomach, and at times marked pylorospasm following trauma of the gallbladder, appendix and duodenum, which they regard as reflex phenomena.

3. Cannon, W. B.: *Mechanical Factor of Digestion*, New York, Longmans Green & Company, 1911.

4. White, F. W.: *Effect of Stimuli from Lower Bowel on the Rate of Emptying of the Stomach*, *Am. J. M. Sc.* **156**:184, 1918.

5. Monroe, R. T., and Emory, E. S.: *The Effect of Irritation of the Colon on the Emptying Time of the Stomach*, *Am. J. M. Sc.* **177**:389, 1929.

6. Hughson, Walter: *Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs*, *Arch. Surg.* **11**:136 (July) 1925.

7. Barber, W. H., and Stewart, George D.: *Further Observations on Reflex Gastric Hypermotility*, *Proc. Soc. Exper. Biol. & Med.* **17**:155, 1919.

The investigation at this point was extended to the patient. A balloon was introduced into the pyloric portion of the stomach and connected with a kymograph during a period in which the subject was free from distress. After the gastric activity was recorded for a control period, the colon was inflated through a rectal tube. The tone of the stomach was at once increased; coincidentally there was a striking increase in the depth of the peristaltic waves and the appearance of the typical epigastric distress. The pain in each instance occurred simultaneously with the peristaltic waves. Following deflation of the colon, the gastric tone and peristaltic action returned to the original level, and the pain disappeared. Similar results were obtained by atropine without the deflation of the colon. This aspect of the investigation is of particular interest from the standpoint of gastric pain and will be reported more in detail in this connection. It is felt that these results explain the epigastric pain associated with an irritable colon.

COMMENT

The reports here cited of the investigations of the reflex connection between the stomach and the colon have led to diverse conclusions. In the observation of White, and in those of Monroe and Emory, attention was focused on the emptying time of the stomach, and a significant alteration in this feature was not obtained. White indicated that a gastric retention is seldom associated with a pathologic condition of the colon. It was likewise rarely noted in our studies of the gastric manifestation of an irritable colon. It is to be recalled that in the latter study a pyloric spasm and an increase in the peristaltic action of the stomach were the most prominent roentgen observations. In this connection, Hughson reported that a traumatization of any abdominal viscus in the dog by surgical procedure, prolongs the emptying time of the stomach approximately 67 per cent for a period of about two weeks in spite of an increase in the speed of the contraction waves. Clinical and experimental observation therefore indicate that a study of the emptying time of the stomach alone is not a reliable guide in the investigation of the reflex connection between the colon and the stomach. On the other hand, the evidence points to an increase in the tone, particularly of the pyloric portion of the stomach and to an increase in the peristaltic action as the most significant indication of a stimulation from the colon.

The observations of Percy and Van Liere appear to be opposed to those made in the present investigation. The character of the stimulation employed is, however, not comparable. The brief periods of inhibition of the gastric contraction shown in their illustrative experiment are similar to those frequently observed in the unanesthetized dog on slight manipulation of the gastro-intestinal tract. These periods

inflation and immediately subsided with the release in tension. This increase in tone and in the peristaltic action of the stomach, regardless of the intensity, was abolished by atropine. The reflex stimulation of the stomach from the irritation of the colon was observed, regardless of the depth of the barbitol anesthesia. Comparable results were obtained when the irritation was limited to the appendix, and the response to atropine was identical (chart 2).

The reflex connection between the gallbladder and the stomach was studied in a similar manner. During the recording of the control period of the gastric activity, the gallbladder was aspirated. The remaining bile was removed by means of small cotton pledgets through an incision in the fundus of the gallbladder. The neck of the gallbladder was finally occluded by cotton to prevent the possibility of the croton oil

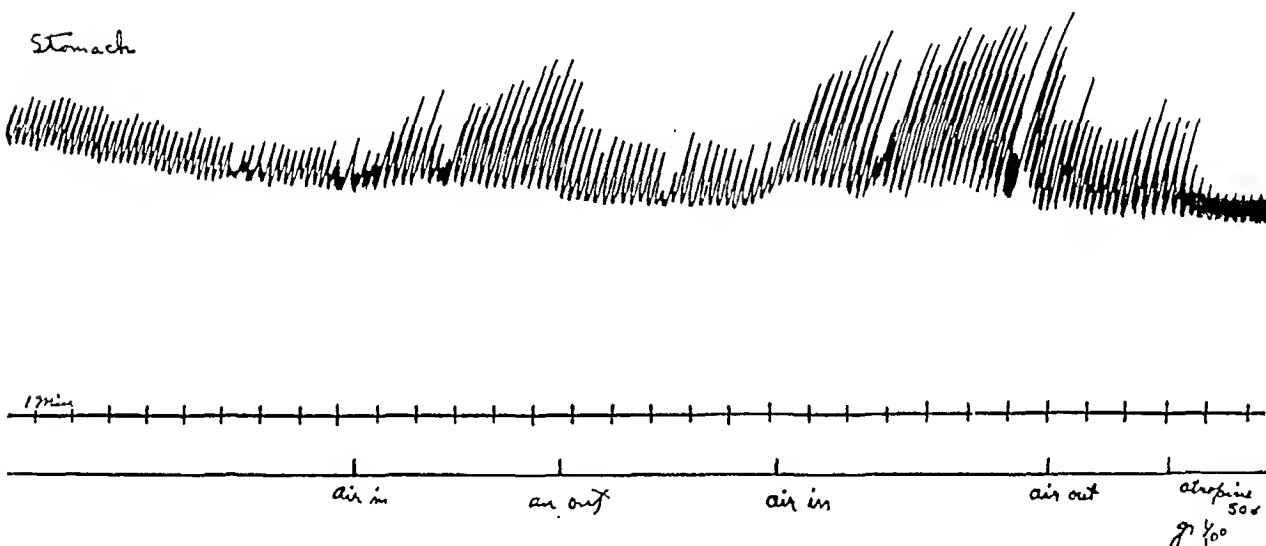


Chart 2.—Changes in the gastric activity following the introduction of croton oil into the appendix. During the increased gastric activity, the irritant in the appendix had induced circular areas of marked constriction. The results in this experiment were similar to those observed following the introduction of the irritant into the colon and gallbladder. In all instances there was a prompt response to the administration of atropine. The time of the administration of the atropine is indicated by the arrow.

passing down the duct. In some instances the common duct was ligated.

During the aforementioned manipulation of the gallbladder, there was no appreciable change in the tone or peristaltic action of the stomach. Croton oil was then applied to the mucosa of the gallbladder by a small cotton swab. After a few minutes there was an increase in the size and depth of the peristaltic waves, comparable to those observed following the application of the irritant to the colon. Here again the induced gastric activity was abolished by atropine.

THE ALKALINE TIDE AS A METHOD OF STUDYING GASTRIC ACIDITY*

ROGER S. HUBBARD, PH.D.

CLIFTON SPRINGS, N. Y.

In 1926 a series of tests on the urine of patients suffering from achlorhydria was reported.¹ It was shown that little or no increase in alkalinity developed in such subjects after a standard meal, but that when normal subjects used as controls were studied by the same technic, the urine usually showed an alkaline tide; that is, it became more alkaline than it had been before the meal. The difference between the two types of cases was clearly shown by the average figures. This indicated that the secretion of hydrochloric acid by the stomach was the usual cause of the increase in alkalinity observed, as had been claimed by many observers since Bence-Jones² first described these variations in acidity.³ Similar work by Ackman⁴ and Davies⁵ has furnished confirmation of this thesis.

In addition to these studies of the physiology involved, it was suggested that the test might be adapted to the indirect study of gastric secretion, and the following procedure was recommended for this purpose. The patient was aroused at 7 o'clock and directed to empty the bladder. This specimen was discarded. Thereafter hourly specimens were collected until 1 p. m. A meal, consisting of two slices of toast, a pat of butter, a glass of milk, a glass of water and an egg, was fed between 8 and 9 o'clock. There were available for analysis six hourly specimens, one collected before the meal, one during the period when the meal was fed and four successive ones following it. The reaction of each was determined soon after it was voided. From a study of the

* Submitted for publication, July 5, 1930.

1. Munford, S. A., and Hubbard, R. S.: The Alkaline Tide in Achlorhydria, *J. A. M. A.* **87**:922 (Sept. 18) 1926.

2. Bence-Jones, H.: Variations in Earthy and Alkaline Phosphates of the Urine, *Phil. Tr., London* **135**:335, 1845; cited by Watson: *Canad. M. A. J.* **15**:32, 1925; *Phil. Tr., London* **139**:235, 1849; cited by Fiske (footnote 3, first reference).

3. Fiske, C. J.: Observations on the "Alkaline Tide" After Meals, *J. Biol. Chem.* **49**:163, 1921. Campbell, C. J.: Ammonia Excretion, Amino-Acid Excretion, and the Alkaline Tide in Singapore, *Biochem. J.* **14**:603, 1920.

4. Ackman, F. D.: The Relations Between Gastric Acidity and the Hydrogen Concentration of the Urine with a Study of the Effect of Histamine, *Canad. M. A. J.* **15**:1099, 1925.

5. Davies, D. T.: Some Observations on Gastric Secretion and Its Relation to the Urinary Reaction, *Brit. J. Exper. Path.* **10**:1, 1929.

are regarded as transitory and of an entirely different nature than those herewith reported.

In the present investigation, a reflex stimulation of the stomach from the colon, appendix and the gallbladder was demonstrated. This effect which was indicated by an increase in the tone, particularly of the pyloric portion, and by an increase in the depth of the peristaltic waves was completely abolished by atropine. Hughson attributed a similar alteration in the gastric activity to a peritoneal irritation. In the present study, however, all operative procedures incident to the experiment were completed prior to the registration of the control curve, and thus the possibility of an irritation from the peritoneum producing the results was eliminated. These observations on patients are in line with the experimental studies on the dog, and they constitute a further demonstration of the reflex connection between the colon and the stomach.

one of which was closely like the other five. Column I shows the flat curve with a rather high degree of acidity frequently found in cases of achlorhydria. Superimposed on this there is not infrequently an early period of alkalinity (column II) that is often prolonged well into the morning (column III). Results typical of those expected if the stomach secretes hydrochloric acid are given in column IV. Here there is no early morning period of alkalinity, but changes similar to those expected if the stomach secreted hydrochloric acid develop after the meal is fed, and an alkalinity of the urine results from the changes in the body fluids produced. Results in column V are essentially similar and can easily be interpreted, although the figures are not quite as regular as those just discussed. It is evident that if there are two normal causes of a decreased acidity in morning urine they must fre-

TABLE 1.—*Irregularities Due to Achlorhydria and an Early Morning Period of Alkalinity**

Hour	I 0 Hydro- chloric Acid <i>p_H</i>	II 0 Hydro- chloric Acid <i>p_H</i>	III 0 Hydro- chloric Acid <i>p_H</i>	IV Hydro- chloric Acid + <i>p_H</i>	V Hydro- chloric Acid + <i>p_H</i>	VI Hydro- chloric Acid + <i>p_H</i>	VII Hydro- chloric Acid + <i>p_H</i>	VIII Hydro- chloric Acid + <i>p_H</i>
Before meal.....	5.4	6.3	7.3	5.4	5.6	7.1	7.5	7.8
Meal time.....	5.4	5.3	6.9	5.9	5.6	5.9	7.6	7.8
0 to 1 after.....	5.4	5.3	6.1	6.2	5.7	5.7	6.1	7.6
1 to 2 after.....	5.3	5.3	5.7	7.4	6.9	6.3	7.3	7.6
2 to 3 after.....	5.4	5.3	5.4	6.9	6.9	7.1	7.5	7.8
3 to 4 after.....	5.3	5.3	5.4	5.9	5.4	6.4	6.9	7.6

* Each column gives the results obtained by averaging a series of specimens from six different specimens.

quently operate in the same patient. Column VI contains results that illustrate this fact. Figures of this kind are not difficult to interpret, because the early morning period of alkalinity can be quite clearly differentiated from the one that follows the meal. Sometimes, however, the two curves seem to fuse more or less completely. Examples are given in column VII, in which a single specimen with an acid reaction separates two periods of marked alkalinity, and in column VIII in which the reaction is uniformly alkaline throughout. Such results, when obtained in any particular case, are hard to interpret in terms of the clinical condition of the patient, for while in general they seem to be due to the aforementioned causes, in any given case the same results may be brought about in an entirely different manner.¹¹ If the activity of the patient is reduced by keeping him in bed, and respiratory

11. Hubbard, R. S., and Allison, C. B.: A Study of Continued Alkalinity of Morning Urine, *Proc. Soc. Exper. Biol. & Med.* **27**:212, 1929; Clifton M. Bull. **16**:6, 1930.

results it was suggested that if one specimen was more alkaline than any collected previously by 1.0 p_H , or if any two were more alkaline than a previous specimen by 0.5 p_H , a tide was present. If the average reaction was alkaline, that is, if the p_H was greater than 7.0, the test should be regarded as unsatisfactory, because Marshall⁶ has shown that the reactions of such specimens cannot be determined accurately. If a tide was present in the urine, it implied that acid was secreted by the stomach. Comparison of the method with the direct analysis of gastric contents showed that there was agreement in about 80 per cent of the studies.

In the present paper the author wishes to discuss the application of this technic in the light of further experience with it, based on a study of 365 tests on 296 subjects. This discussion can conveniently be divided into two parts: first, a consideration of the general forms of the curves obtained, and second, a presentation of individual cases representing the value and limitations of the method.

In general, the results have confirmed the physiologic principal on which the test is based, for the tide shown by normal subjects⁷ was quite regularly present when secretion of acid followed the ingestion of a test meal⁸ but was absent in cases of achlorhydria. At the same time it became obvious that results were frequently irregular and hard to interpret. An analysis of the various types of curves was made,⁹ and it was concluded that there was frequently an early morning period of alkalinity before any meal was fed that affected the test.¹⁰ Table 1 shows the irregularities resulting from the operation of these two causes. Each column gives results obtained by averaging the results obtained from a series of specimens from six different patients, each

6. Marshall, E. K., Jr.: The Effect of Loss of Carbon Dioxide on the Hydrogen Ion Concentration of Urine, *J. Biol. Chem.* **51**:3, 1922.

7. Wilson, D. W.: Neutrality Regulation in the Body, *Physiol. Rev.* **3**:295, 1923. Hubbard, R. S., and Munford, S. A.: Presence of the "Alkaline Tide," *J. A. M. A.* **80**:304 (Feb. 3) 1923. Muschat, M.: The Effect of Changes in Regime upon the Urine Alkaline Tide in Normal Individuals, *J. Clin. Investigation* **2**:245, 1925. Hubbard, R. S., and Steele, T. M.: Variations in the Morning Alkaline Tide of Normal Individuals, *J. Biol. Chem.* **84**:199, 1929.

8. Rehfuess, M. E.: A New Method of Gastric Testing, with a Description of a Method for the Fractional Testing of the Gastric Juice, *Am. J. M. Sc.* **147**: 848, 1914. Lyons, B. B. V.; Barth, H. J., and Ellison, R. T.: Clinical Gastric Analysis with Detail of Method and a Consideration of the Maximum Information to be Obtained, *New York M. J.* **114**:272, 1921.

9. Hubbard, R. S.: The Reaction of the Morning Urine, *J. Biol. Chem.* **84**:191, 1929.

10. Leathes, J. B.: Renal Efficiency Tests in Nephritis and the Reaction of the Urine, *Brit. M. J.* **2**:165, 1919; Renal Function, a Determination of Its Degree, *Lancet* **2**:933, 1920. Watson, E. M.: The Cause of the Matutinal Tide in Urine, *Canad. M. A. J.* **15**:32, 1925. Hubbard, R. S.: Changes in the Reaction of Urine on Awakening, *Am. J. Physiol.* **91**:618, 1930.

The third case, shown in table 4, is an example of those cases in which a study of the tide gives more reliable information than an analysis of the gastric contents after the usual test meal. Another similar case has been reported previously.¹⁶ The results of a gastric analysis suggested that the stomach did not secrete hydrochloric acid,

TABLE 2.—*Complete Concordant Results in Gastric Analysis and Alkaline Tide Test in a Case of Achlorhydria*

Gastric Analysis			Histamine Test					
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.			
0.....	0	15	0.....	0	9			
30.....	0	7	20.....	0	7			
45.....	0	5	40.....	0	8			
60.....	0	6	60.....	0	6			
75.....	0	8	1.5 mg. ergamine* phosphate used					
105.....	0	9						
135.....	0	?						
Alkaline Tide Test †								
			Time					
			7-8	8-9	9-10	10-11	11-12	12-1
pu.....			5.4	5.3	5.3	5.3	5.3	5.5

* Ergamine is beta-iminazolethylamine hydrochloride.

† Results of gastric studies are expressed as cubic centimeters of tenth-normal acid in 100 cc. gastric contents.

TABLE 3.—*Showing Agreement of Gastric Analysis and Alkaline Tide Test*

Gastric Analysis*			Histamine Test					
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.			
75.....	0	12	0.....	0	16			
			20.....	0	18			
			40.....	0	23			
			60.....	5	27			
			1.5 mg. ergamine phosphate used					
Alkaline Tide Test								
			Time					
			7-8	8-9	9-10	10-11	11-12	12-1
ph.....			5.2	5.0	5.0	5.7	5.2	5.0

* Results of gastric studies are expressed as cubic centimeters of tenth-normal acid in 100 cc. gastric contents. The gastric specimen was obtained through a large tube passed after an Ewald test meal.

although the high figures obtained when the total acid was determined make such an interpretation questionable. When histamine was given, free hydrochloric acid was found in normal concentration. I believe that two causes may lead to such results. If the stomach produces acid but it is neutralized by alkaline secretions or mucus, the urine should

16. Hubbard, R. S.: Variations in Gastric Acidity and in the Alkaline Tide in Urine, a Discussion of a Case, *Clifton M. Bull.* 14:7, 1928.

variations, which form one of the causes of variations in urinary acidity,¹² are thus reduced to a minimum, anomalous results are still encountered.¹³

It is obvious from the preceding discussion that results that cannot be interpreted or that can be interpreted only with considerable uncertainty are not infrequent. It seems worth while to present also a series of selected cases illustrating the various types of observations to show the value and limitations of the method when the results are characteristic. For this purpose cases in which the results of studies with histamine¹⁴ were available have been selected. Since histamine is used in this clinic only when routine gastric analysis shows the absence of hydrochloric acid, and since in general determinations of the alkaline tide were not carried out except when the presence of achlorhydria was suspected, no strictly normal case is included in the series. For such results the reader is referred to previous publications,¹⁵ and to table 1, columns IV and V. The series does include complete concordant results in a case of achlorhydria, and these results are given in table 2. The urine of this patient showed no change in reaction during the morning period, and no acid was secreted into the stomach under the stimulus of any of the methods used.

The case summarized in table 3 also shows satisfactory agreement among the three methods of studying gastric acidity. No hydrochloric acid was present in the stomach an hour and a half after a test meal, but an hour after histamine was given a trace of the free acid could be detected. In the study of the alkaline tide a slight increased alkalinity was found in one specimen obtained after the meal. This change was so slight that no significance can properly be attached to it, and, according to the criteria laid down in the preceding article,¹ no tide was present. It is obvious that such results must be expected when the gastric acidity is as low as in this case.

12. Collip, J. B., and Backus, P. L.: The Effect of Prolonged Hyperpnoea on the Carbon Dioxide Combining Power of the Plasma, the Carbon Dioxide Tension of the Alveolar Air, and the Excretion of Acid and Basic Phosphate and Ammonia by the Kidney, *Am. J. Physiol.* **51**:568, 1920. Grant, S. B., and Goldam, A.: A Study of Forced Respiration: Experimental Production of Tetany, *Am. J. Physiol.* **52**:209, 1920.

13. Hubbard, R. S., and Steele, T. M. (footnote 7, fourth reference).

14. Dobson, H. V.: Effect of Histamin on Gastric Secretion, *J. A. M. A.* **84**:158 (Jan. 17) 1925. Schneider, J. P., and Carey, J. B.: The Clinical Significance of Primary Achlorhydria, *J. A. M. A.* **91**:1763 (Dec. 8) 1928.

15. Hubbard, R. S.; Munford, S. A., and Allen, E. G.: Gastric Secretion and the Alkaline Tide in Urine, *Am. J. Physiol.* **68**:207 (Nov. 23) 1924. Hubbard, R. S., and Allen, E. G.: Simultaneous Determinations of Gastric Acidity and the Alkaline Tide in Urine, *Arch. Int. Med.* **35**:586 (May) 1925.

in table 5. The tide obtained was not wholly satisfactory but it suggested that the stomach secreted hydrochloric acid, while all of the direct studies carried out failed to show any formation of that compound. No adequate explanation can be offered for such observations. Either the direct methods used for studying gastric secretion are not wholly satisfactory—I do not believe that there is sufficient evidence to justify such a conclusion—or there may be some cause independent of the secretion of hydrochloric acid by the stomach that sometimes produces changes in urinary reaction that are indistinguishable from those considered as typical tides. A few experiments suggest that the second alkaline tide of the day—that which follows the noon meal—may give more reliable information concerning the presence or absence of gastric secretion than does the first one, but at present the number of studies

TABLE 5.—*Contradictory Results Obtained in the Same Patient*

Gastric Analysis			Histamine Test*					
Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.	Time, Minutes	Hydrochloric Acid, Cc.	Total Cc.			
0.....	0	9	0.....	0	5			
30.....	0	5	20.....	0	8			
45.....	0	6	40.....	0	10			
60.....	0	4	60.....	0	8			
75.....	0	5	1.5 mg. ergamine phosphate used					
105.....	0	9						
135.....	0	10						
Alkaline Tide Test†			Time					
			7-8	8-9	9-10	10-11	11-12	12-1
pH.....			...	6.1	6.2	...	7.1	7.4

* Gastric analysis and histamine test agree.

† Results are expressed as cubic centimeters of tenth-normal acid per 100 cc. gastric juice.

available are too few to serve as a basis for conclusions on their significance.

Errors of the opposite sort, the absence of a tide when the stomach secretes hydrochloric acid, are present in about 20 per cent of the cases studied. One large group of patients in whom such observations were made, were subjects with various conditions affecting gastric secretion. There may be so marked a degree of hypochlorhydria that variations in the acid-base balance in the body are so slight that no changes in the reaction of the urine result from it. An essentially similar condition exists when the concentration of hydrochloric acid is normal but the amount of fluid secreted is small. Here again little variation in the reaction of the body fluids may result from gastric secretion, because those changes depend on the actual amount of acid withdrawn from the tissues and the resultant liberation of an approximately equivalent amount of base in them. A third group of cases in which discrepancies of this sort are easily understood includes those in which there is a

nevertheless show the normal tide. Another possibility is that the secretion of hydrochloric acid has been completely inhibited by some influence induced by the presence of the tube,¹⁷ but that secretion may proceed normally when no tube is present, and that, therefore, there may be a normal tide.

When a typical alkaline tide is present in a case apparently showing achlorhydria, the gastric analysis should be questioned and careful investigations carried out before a diagnosis is made. Can the alkaline tide observations be accepted as of final value under such conditions? The answer to this question is probably no, as far as one can tell at present. My associates and I have found very few cases—three at most

TABLE 4.—Case in Which Study of the Alkaline Tide Gave More Accurate Information Than Analysis of the Gastric Contents After the Usual Test Meal

Gastric Analysis			Histamine Test*					
Time, Minutes	Hydrochloric Acid, Ce.	Total Ce.	Time, Minutes	Hydrochloric Acid, Ce.	Total Ce.			
0.....	0	?	0.....	0	5			
30.....	0	11	20.....	0	10			
45.....	0	40	40.....	36	58			
60.....	0	30	60.....	31	50			
75.....	0	25	1.5 mg. ergamine phosphate used					
105.....	0	19						
135.....	0	?						
Alkaline Tide †			Time					
			7-8	8-9	9-10	10-11	11-12	12-1
pH.....			5.3	5.3	6.1	6.2	6.6	5.8

* Histamine test and alkaline tide test agree.

† Results of gastric studies are expressed as cubic centimeters of tenth-normal acid in 100 cc. of gastric contents.

—when such an interpretation would probably have been incorrect. In these three cases fairly typical alkaline tides were present in the urine, but no hydrochloric acid was found in the contents of the stomach after histamine was injected. None of these cases has shown the clean-cut clinical picture frequently seen in achylia gastrica.¹⁸ It seems proper, nevertheless, to accept them as true cases of achlorhydria until such indirect studies as have been carried out in the clinic can be confirmed by some other method of investigation. Fairly complete experiments showing such contradictory results have been carried out on one patient and reported elsewhere.¹⁹ Studies in another case are given

17. Kahn, G., and Stokes, J., Jr.: The Effect of the Passage of the Stomach Tube on Titratable Acidity and *pH* of Gastric Contents, *Am. J. Dis. Child.* **32**: 667 (Nov.) 1926.

18. Collip and Backus (footnote 12, first reference).

19. Hubbard, R. S., and Case, C. E.: Presence of the Alkaline Tide in a Case of Achlorhydria, *Proc. Soc. Exper. Biol. & Med.* **27**:327, 1930.

METABOLISM OF OBESITY

VIII. BASAL METABOLISM AND INSENSIBLE PERSPIRATION DURING A PERIOD OF REDUCING WEIGHT *

CHI CHE WANG, PH.D.

SOLOMON STROUSE, M.D.

AND

MARIE ANDERSCH, B.S.

CHICAGO

Owing to the lack of adequate provisions for prolonged metabolic work on adults during a period of reducing weight, our previous studies of this series had been made on outpatients only. An extensive investigation was conducted on three obese women, one with diabetes, during a period of eight months in 1928. The subjects were kept in a special ward provided with a kitchenette and facilities for collecting and storing excreta. They were given freedom to lead a normal life and were permitted to go about as they pleased. However, they were under the constant supervision of an attendant assigned to this task. At no time were they allowed free access to foods.

During the experimental period the subjects received a diet containing 20 Gm. of butter per twenty-four hours, 1 Gm. of protein and sufficient carbohydrate to make a total of 20 calories per kilogram of ideal weight per twenty-four hours. Based on our investigations conducted on a number of normal women, the foregoing diet should contain approximately 50 per cent of the caloric value required by these subjects according to their ideal weights. In the case of the subject with diabetes, sufficient insulin was given to keep her urine always free from sugar; the dosage varied from 30 units at the beginning to 8 units at the end of the experiment. As this subject demonstrated a rapid decrease in basal metabolism in the course of reducing weight, she was also given thyroid treatment during the latter part of the experiment.

This investigation covered the determination of basal metabolism, insensible perspiration, water balance and protein metabolism of the three subjects. The present paper deals with the basal metabolism and the insensible perspiration. The chemical procedure and the results of the latter half of the investigation will be reported in a later communication.

* Submitted for publication, April 23, 1930.

* From the Medical Clinic and the Nelson Morris Memorial Institute for Medical Research of Michael Reese Hospital. Aided by the Otto Baer Fund and the fund contributed jointly by Judge Hugo Pam and Miss Carrie Pam.

very rapid gastric emptying time. In these the acid material probably enters the intestine and is once more reabsorbed soon after it is formed, so that changes in the reaction of the tissues is of short duration.

Besides such cases as these in which the conditions governing secretion and reabsorption of hydrochloric acid probably influence the results, there are certain diseases that may cause an absence of a tide in a subject with normal gastric acidity. One of these diseases is cystitis. Persons suffering from this condition are not suitable subjects for the test, because the reaction of the urine may result from the action of bacteria in the bladder rather than from variations in the acid-base balance in the body. Nephritis may also apparently sometimes give rise to misleading results. Leathes²⁰ and McCorvie²¹ have shown that in this condition the reaction of the urine does not respond in the usual way to variations in the conditions in the blood. Whether there are other factors that may seriously affect the reaction of the urine in a similar way, remains uncertain. Among the possibilities is the modifying influence of the phosphates present as buffers in the urine. The work on this subject recently reviewed by Rannenbergh²² suggests that variations in the amounts of these compounds may sometimes be of importance in modifying the reaction of the urine.

CONCLUSION

A study of the urine in a series of cases has shown that the presence or absence of an alkaline tide may frequently be of aid in the study of gastric conditions. When a tide is present after a meal, hydrochloric acid can almost always be demonstrated in the gastric juice. In about 80 per cent of those subjects who do not show an alkaline tide, hydrochloric acid is either absent from the gastric juice or is present in very low concentration.

Certain limitations exist to the usefulness of the test. It seems to be impossible to distinguish between a normal secretion and a hypersecretion of hydrochloric acid by this method.²³ It is frequently difficult to interpret the results obtained because of their irregular nature. The test is valueless in cystitis and nephritis. Apparently the alkaline tide should not be relied on alone to distinguish between the true and false achylia; however, if a tide is present, such a diagnosis should be made only after thorough study, including the use of histamine.

20. Leathes (footnote 10, first and second references).

21. McCorvie, J. E.: Studies on the Morning Alkaline Tide of Urine in Normal Persons and in Patients with Nephritis, *J. Clin. Investigation* **2**:35, 1925.

22. Rannenbergh, E.: Die Schwankungen der Wasserstoffionenkonzentration des Harns im Verlaufe eines Tages, *Arch. f. d. ges. Physiol.* **212**:601, 1926.

23. Dodds, E. C.: Variations in Some of the Urinary Constituents and the Alveolar CO₂ in Relation to Meals, *Brit. J. Exper. Path.* **4**:13, 1923.

TABLE 1.—*Daily Basal Heat Production—Continued*

Subject: E. S.; height, 150.9 cm.; age, 35 years; normal weight, 55.9 Kg.

Date	Weight			Heat Production						Pulse Rate	Thyroid Extract, Gr.
	Kg.	Per- Daily Vari- tion, Kg.	centage Over Normal Weight	R. Q.	Calo- ries per Sq.M. per Hour	Percent- age of Devia- tion from Normal	Calo- ries per 24 Hours	Percent- age of Devia- tion from Normal	Calo- ries per 24 Hours		
Dec. 8	72.4	-0.2	29.5	0.721	32.9	-11.3	1,330	-10.0	18.4	54	1
10	72.3	-0.1	29.3	0.733	31.6	-14.6	1,273	-13.0	17.6	62	2
11	72.4	+0.1	29.5	0.746	33.6	- 9.1	1,358	- 7.5	18.8	66	2
12	72.2	-0.2	29.1	0.749	33.9	- 8.3	1,369	- 6.4	19.0	62	2
13	72.5	+0.3	29.7	0.761	35.8	- 3.2	1,439	- 1.1	19.9	64	2
15	72.3	-0.2	29.3	0.735	36.2	- 2.1	1,463	± 0.0	20.2	74	2
26	71.8	28.4	0.867	35.1	- 5.2	1,406	- 3.6	19.6	62	2
27	70.9	-0.9	26.8	0.832	34.3	- 6.9	1,377	- 5.0	19.4	58	2
28	70.9	±0.0	26.8	0.884	34.6	- 6.4	1,387	- 4.3	19.6	56	2
29	70.7	-0.2	26.4	0.781	36.7	- 0.8	1,468	+ 1.5	20.8	68	2
31	70.1	-0.6	25.4	0.860	34.3	- 7.2	1,368	- 5.1	19.5	68	2
Jan. 2	69.8	-0.4	24.8	0.798	35.1	- 5.1	1,397	- 2.9	20.0	74	2
3	69.8	±0.0	24.8	0.785	35.8	- 3.3	1,423	- 1.1	20.4	70	2
4	69.5	-0.2	24.4	0.701	35.9	- 3.1	1,424	- 0.8	20.5	76	...
5	69.2	-0.3	23.8	0.779	37.1	+ 0.2	1,470	+ 2.6	21.2	72	...
7	69.3	+0.1	24.0	0.779	35.9	- 3.1	1,422	- 0.8	20.5	66	...
8	69.3	±0.0	24.0	0.726	39.2	+ 6.0	1,555	+ 8.4	22.4	72	...
9	69.5	+0.2	24.4	0.719	38.8	+ 4.9	1,541	+ 7.2	22.2	72	...

During the period of reducing weight, the study of basal metabolism of the three subjects, including eighty-nine experiments on one and seventy-three on another, was made within four months. Twenty-eight experiments were conducted on the third subject during an interval of a month. An attempt was made to take daily observations, but owing to the lack of cooperation on the part of the subjects, the work was interrupted frequently. Consequently, no observations were made on Sundays or on days when for various reasons the patients were in a contradictory mood and offered excuses for not taking the test. At the beginning of the experiment the weights of the three subjects were 80.3, 95 and 108.4 kilograms, with a deviation from standard of 43.5, 54.7 and 95.4 per cent, respectively. The ages were 35, 23 and 21 years.

Heat production was measured by a Tissot gasometer in connection with a Haldane gas analysis apparatus as described in a previous communication.¹ All experiments were conducted after a fast of at least fourteen hours and a rest period of thirty minutes.

1. Strouse, S.; Wang, C. C., and Dye, M.: Studies on the Metabolism of Obesity: II. Basal Metabolism, Arch. Int. Med. 34:275 (Sept.) 1924.

TABLE 1.—Daily Basal Heat Production

Subject: E. S.; height, 150.9 cm.; age, 35 years; normal weight, 55.9 Kg.

Subject: Dr. W. H											
---	--	--	--	--	--	--	--	--	--	--	--

TABLE 3.—*Basal Heat Production*

Subject: H. M.; height, 159.4 cm.; age, 21 years; normal weight, 55.5 Kg.

Date	Kg.	Weight			Heat Production						Pulse Rate
		Daily Variation, Kg.	Per-centage Variation Over Normal	R. Q.	Calo-ries per Sq.M. per Hour	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	Percent- age of Devia- tion from Normal	Calo-ries per Kg. per 24 Hours		
May 29.....	108.4	95.4	0.688	37.5	+ 1.4	1,880	— 0.5	17.4	70	
30.....	108.4	±0.0	95.4	0.681	37.2	+ 0.5	1,865	— 1.2	17.2	68	
31.....	108.0	—0.4	94.6	0.736	35.4	— 4.3	1,768	— 6.2	16.4	66	
June 1.....	107.6	—0.4	93.9	0.734	35.0	— 5.3	1,750	— 7.0	16.3	65	
2.....	107.6	±0.0	93.9	0.741	33.4	— 9.8	1,666	—11.4	15.5	66	
4.....	107.0	—1.0	92.8	0.715	34.9	— 5.7	1,736	— 7.4	16.2	64	
5.....	107.0	±0.0	92.8	0.732	33.8	— 8.6	1,683	—10.2	15.2	66	
6.....	107.0	±0.0	92.8	0.700	35.5	— 4.2	1,764	— 5.9	16.5	66	
7.....	107.2	+0.2	93.2	0.708	33.2	—10.3	1,652	—12.0	15.4	68	
9.....	105.8	—1.4	90.7	0.699	34.8	— 6.0	1,727	— 7.4	16.3	66	
11.....	106.5	—0.3	91.9	0.744	34.9	— 5.6	1,738	— 7.1	16.3	64	
12.....	106.3	—0.2	91.5	0.742	32.8	—11.2	1,633	—12.6	15.4	63	
13.....	106.1	—0.2	91.1	0.754	33.6	— 9.1	1,672	—10.4	15.8	62	
14.....	105.9	—0.2	90.8	0.731	34.0	— 8.1	1,690	— 9.4	16.0	60	
15.....	105.7	—0.2	90.5	0.732	35.2	— 4.8	1,750	— 6.1	16.5	64	
16.....	105.4	—0.3	90.0	0.688	36.1	— 2.6	1,791	— 3.7	17.0	66	
18.....	105.3	—0.7	89.7	0.644	33.8	—11.4	1,670	—10.1	15.9	70	
19.....	105.0	—0.3	89.2	0.684	35.4	— 4.3	1,751	— 5.6	16.7	68	
20.....	105.0	±0.0	89.2	0.683	32.7	—11.6	1,616	—12.9	15.4	66	
21.....	104.7	—0.3	88.7	0.727	34.2	— 7.5	1,691	— 8.7	16.2	66	
22.....	104.1	—0.6	87.6	0.694	34.2	— 8.6	1,633	— 8.9	16.2	66	
23.....	103.9	—0.2	87.3	0.733	36.5	— 1.5	1,792	— 2.9	17.3	68	
25.....	103.5	—1.2	86.5	0.742	33.9	— 5.6	1,656	—10.1	16.0	64	
26.....	103.7	+0.2	86.9	0.717	34.6	— 6.3	1,696	— 8.0	16.4	68	
27.....	103.5	—0.2	86.5	0.695	35.8	— 3.1	1,754	— 4.8	17.0	72	
28.....	102.9	—0.6	85.4	0.708	33.3	— 9.9	1,624	—11.5	15.8	66	
29.....	102.5	—0.4	84.5	0.740	34.7	— 6.5	1,675	— 8.6	16.3	66	
30.....	102.6	+0.1	84.9	0.743	37.9	+ 1.4	1,845	+ 0.6	18.0	64	

TABLE 4.—*Weekly Averages of Daily Basal Heat Production*

Subject: E. S.; height, 150.9 cm.; age, 35 years; normal weight, 55.9 Kg.

Weeks	Weight			Heat Production						Pulse Rate	Thyroid Extract, Gr.
	Kg.	Daily Loss, Kg.	Percentage Variation Over Normal Weight	R. Q.	Calo-ries per Sq.M. per Hour	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	Percent- age of Devia- tion from Normal	Calo-ries per Kg. per 24 Hours		
1	79.7	—0.2	42.4	0.693	39.0	+ 5.9	1,640	+ 7.5	20.7	71	...
2	79.1	—0.1	41.4	0.773	35.1	— 5.1	1,472	— 3.6	18.6	69	...
3	79.9	—0.3	42.9	0.762	37.7	+ 1.8	1,583	+ 3.2	19.9	72	...
4	79.6	±0.0	42.5	0.724	34.1	— 7.9	1,432	— 6.6	18.0	69	...
5	78.5	—0.2	40.4	0.723	31.4	—15.2	1,321	—13.5	16.8	62	...
6	77.7	—0.2	39.0	0.723	30.8	—16.9	1,287	—15.2	16.6	59	...
7	77.3	+0.1	38.3	0.750	30.8	—17.2	1,278	—15.9	16.5	60	...
8	76.2	—0.2	36.3	0.755	31.5	—14.9	1,304	—13.1	17.1	58	...
9	75.4	—0.1	34.9	0.765	30.6	—17.5	1,256	—16.0	16.6	56	...
10	75.0	—0.2	34.1	0.751	31.4	—15.2	1,285	—13.5	17.2	53	1.0
11	73.4	—0.2	31.3	0.754	31.7	—13.9	1,281	—13.2	17.5	58	1.0
12	73.1	—0.1	30.7	0.725	32.2	—12.9	1,304	—11.1	18.0	62	1.0
13	72.6	±0.0	29.9	0.762	31.2	—15.8	1,260	—14.1	17.4	57	1.0
14	72.3	±0.0	29.4	0.745	34.2	— 7.5	1,380	— 5.6	19.1	66	2.0
15	71.1	—0.4	27.1	0.841	35.2	— 4.8	1,409	— 2.9	19.9	58	2.0
16	69.7	—0.3	24.6	0.785	35.6	— 3.7	1,416	— 1.5	20.3	72	2.0
17	69.4	+0.1	24.1	0.741	38.0	+ 2.6	1,506	+ 4.9	21.7	70	2.0
Average	—0.14	33.6	— 9.3	1,377	— 7.7	18.4

TABLE 2.—Daily Basal Heat Production

Subject: C. B.; height, 168.9 cm.; age, 23 years; normal weight, 61.4 Kg.

Date	Kg.	Weight		R. Q.	Heat Production					Pulse Rate		
		Daily Variation, Kg.	Percentage Over Normal Weight		Calo-ries per Sq.M. per Hour	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	Percent- age of Devia- tion from Normal	Calo-ries per Kg. per 24 Hours			
May	24.....	95.0	54.7	0.877	33.6	— 9.1	1,655	— 6.2	17.4	72	
	25.....	94.3	—0.7	53.6	0.728	35.2	— 4.8	1,732	— 1.4	18.4	70	
	26.....	94.3	+0.0	53.6	0.746	33.9	— 8.3	1,665	— 5.2	17.7	65	
	28.....	94.8	+0.5	54.4	0.765	31.0	—16.3	1,523	—13.6	16.1	64	
	29.....	94.2	—0.6	53.4	0.874	31.4	—15.2	1,539	—12.4	16.3	65	
	30.....	94.2	+0.0	53.4	0.786	34.7	— 6.2	1,701	— 3.0	18.1	64	
	31.....	93.8	—0.4	52.8	0.797	36.2	— 2.1	1,777	+ 1.3	19.0	64	
June	1.....	94.1	+0.3	53.3	0.792	34.1	— 7.7	1,678	— 4.4	17.8	62	
	2.....	93.6	—0.5	52.4	0.792	34.2	— 7.5	1,675	— 4.3	17.9	62	
	4.....	93.0	—0.6	51.5	0.779	31.5	—15.0	1,534	—12.0	16.5	62	
	5.....	93.0	+0.0	51.5	0.808	33.7	— 9.0	1,642	— 5.9	17.7	60	
	6.....	92.8	—0.2	51.1	0.752	32.2	—13.0	1,571	— 9.2	16.9	62	
	7.....	93.0	+0.2	51.5	0.833	35.3	— 4.5	1,723	— 1.2	18.5	62	
	8.....	93.3	+0.3	52.0	0.765	35.1	— 5.2	1,713	— 1.9	18.4	62	
	9.....	93.3	+0.0	52.0	0.861	36.7	— 0.9	1,776	+ 1.1	19.0	60	
	11.....	91.8	—1.5	49.5	0.808	34.2	— 7.5	1,659	— 4.3	18.1	60	
	12.....	91.4	—0.4	48.9	0.755	33.6	— 9.3	1,630	— 5.7	17.8	62	
	13.....	91.5	+0.1	49.0	0.778	32.8	—11.3	1,589	— 8.2	17.4	60	
	14.....	91.6	+0.1	49.2	0.781	32.1	—13.1	1,557	—10.1	17.0	..	
	15.....	91.8	+0.2	49.5	0.739	33.2	—10.3	1,610	— 7.1	17.5	56	
	16.....	91.8	+0.0	49.5	0.719	35.5	— 4.1	1,723	— 0.8	18.8	60	
	18.....	91.5	—0.3	49.0	0.732	34.8	— 5.8	1,687	— 2.5	19.2	60	
	19.....	91.1	—0.4	48.4	0.766	34.7	— 6.3	1,675	— 3.1	18.4	58	
	20.....	90.7	—0.4	47.7	0.776	32.7	—11.1	1,577	— 8.9	17.4	58	
	21.....	91.0	+0.3	48.2	0.719	30.7	—17.0	1,483	—14.0	16.3	60	
	23.....	89.5	—1.5	45.8	0.769	32.8	—11.4	1,572	— 8.1	17.6	56	
	25.....	89.4	—0.1	45.6	0.735	36.3	— 1.8	1,742	+ 1.8	19.5	59	
	26.....	89.9	+0.5	46.4	0.782	33.6	— 9.2	1,615	— 6.3	18.0	60	
27.....	90.1	+0.2	46.7	0.778	36.3	— 2.0	1,744	+ 1.0	19.4	62		
28.....	90.0	—0.1	46.7	0.757	36.7	— 0.8	1,780	+ 3.2	19.8	60		
29.....	89.6	—0.4	45.9	0.784	35.8	+ 3.9	1,830	+ 6.3	20.4	54		
30.....	89.2	—0.2	45.3	0.750	37.3	+ 0.9	1,788	+ 4.6	20.0	54		
July	2.....	83.6	—1.6	44.3	0.761	34.7	— 6.3	1,654	— 2.9	18.8	60	
	5.....	87.6	—1.0	42.7	0.744	37.7	+ 1.8	1,787	+ 5.6	20.4	58	
	7.....	87.1	—0.5	41.9	0.772	36.9	— 0.4	1,749	+ 2.5	20.1	64	
	9.....	86.6	—0.5	41.0	0.778	34.5	— 6.8	1,640	— 1.6	18.9	60	
	10.....	86.9	+0.3	41.5	0.751	37.6	+ 1.5	1,779	+ 6.1	20.5	70	
	11.....	87.0	+0.1	41.7	0.801	31.7	—15.3	1,503	—10.9	17.3	62	
	12.....	87.5	+0.5	42.5	0.778	33.9	— 8.5	1,602	— 5.3	18.3	58	
	18.....	85.9	—1.6	39.9	0.723	34.3	— 7.4	1,614	— 4.1	18.8	58	
	19.....	85.2	—0.7	38.8	0.734	33.9	— 8.5	1,591	— 4.7	18.8	62	
	20.....	86.1	+0.9	40.3	0.840	36.9	— 0.4	1,740	+ 3.6	20.2	66	
	21.....	86.0	—0.1	40.1	0.788	34.6	— 6.4	1,638	— 2.4	19.1	68	
	23.....	85.5	—0.5	39.3	0.830	36.8	— 0.4	1,733	+ 3.6	20.3	64	
	24.....	85.5	+0.0	39.3	0.777	33.1	— 7.9	1,556	— 1.0	18.2	54	
	25.....	85.1	—0.4	38.7	0.766	40.0	+ 8.1	1,876	+11.9	22.1	58	
	26.....	85.4	+0.3	39.1	0.796	33.4	— 6.9	1,581	— 5.4	18.5	56	
	27.....	85.3	—0.1	38.9	0.782	34.2	— 7.5	1,609	— 3.8	18.9	54	
	28.....	85.1	—0.2	38.7	0.772	34.8	— 6.0	1,636	— 2.0	19.2	54	
	30.....	85.5	+0.4	39.3	0.723	35.6	— 3.9	1,674	+0.0	19.6	54	
	31.....	85.2	—0.3	38.8	0.735	34.9	— 5.5	1,643	— 1.9	19.5	58	
	Aug.	16.....	84.4	37.5	0.737	33.9	— 8.5	1,582	— 4.8	18.7	63
		17.....	83.5	—0.9	36.0	0.768	31.9	—13.7	1,483	—10.3	17.8	60
18.....		83.6	+0.1	36.2	0.783	37.0	+0.0	1,723	+ 4.1	20.6	58	
20.....		83.1	—0.5	35.4	0.794	40.2	+ 8.9	1,878	+13.8	22.6	68	
22.....		81.8	—1.3	33.2	0.765	34.5	— 9.4	1,594	— 2.6	19.5	60	
27.....		81.0	—0.8	31.9	0.699	30.3	—18.2	1,392	—14.7	17.2	60	
28.....		81.8	+0.8	33.2	0.717	39.7	+ 7.3	1,834	+12.0	22.4	55	
31.....		81.4	—0.5	32.5	0.724	30.5	—17.6	1,419	—13.1	17.4	55	
Sept. 1.....		81.0	—0.3	32.0	0.725	32.4	—12.6	1,499	— 8.0	18.5	56	
4.....		81.1	+0.1	32.2	0.755	32.2	—13.0	1,499	— 8.1	18.5	56	
5.....	81.0	—0.1	32.0	0.732	33.4	— 9.7	1,548	— 5.0	19.1	54		
6.....	80.8	—0.2	31.6	0.701	33.0	—10.9	1,519	— 6.7	18.8	55		
7.....	81.1	+0.3	32.2	0.724	31.9	—13.9	1,484	— 9.0	18.3	56		
8.....	80.7	—0.5	31.4	0.735	33.6	— 9.1	1,548	— 4.9	19.2	59		
13.....	80.4	—0.2	31.0	0.748	33.8	— 8.9	1,557	— 4.1	19.4	58		
14.....	81.2	+0.7	32.2	0.731	33.6	— 9.2	1,549	— 5.1	19.1	56		
17.....	80.0	—1.2	30.3	0.737	35.6	— 3.1	1,629	+ 0.6	20.4	62		
18.....	79.7	—0.3	29.9	0.723	34.9	— 5.6	1,598	— 0.6	20.0	58		
19.....	79.2	—0.5	29.0	0.768	36.5	— 1.7	1,665	+ 2.7	21.0	60		
20.....	79.2	+0.0	29.0	0.706	38.1	+ 2.7	1,737	+ 7.8	21.9	56		
21.....	79.0	—0.2	28.6	0.706	34.4	— 7.2	1,558	— 3.3	19.7	60		
22.....	79.7	+0.7	29.7	0.726	37.2	+ 0.5	1,695	+ 4.8	21.4	56		

TABLE 7.—*Insensible Perspiration—Continued*

Subject: C. B.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight			Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
			Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.		
10/15	78.4	1.73	33	0.42	19.1	0.72	1.71
10/17	77.9	1.73	35	0.45	20.2	0.68	1.51
10/18	77.8	1.73	30	0.39	17.3	0.71	1.82
10/22	77.6	1.72	29	0.37	16.9	0.70	1.89
10/24	77.4	1.72	25	0.32	14.5	0.71	2.22
10/25	77.6	1.72	28	0.36	16.3	0.69	1.92
10/26	77.5	1.72	29	0.37	16.9	0.73	1.97
10/27	76.9	1.72	25	0.33	14.5	0.64	1.94
10/29	76.6	1.71	32	0.42	18.7	0.70	1.67
10/30	76.5	1.71	26	0.34	15.2	0.72	2.12
10/31	75.9	1.71	24	0.32	14.0	0.68	2.13
11/ 1	76.1	1.71	40	0.53	23.4	0.71	1.34
11/ 2	76.3	1.71	30	0.39	17.5	0.71	1.82
11/ 3	75.8	1.71	27	0.36	15.8	0.75	2.08
11/ 4	75.4	1.71	38	0.50	22.2
11/ 5	75.3	1.71	29	0.39	17.0	0.67	1.72
11/ 6	75.4	1.71	37	0.49	21.6	0.75	1.53
11/ 7	75.6	1.71	27	0.36	15.8	0.68	1.89
11/ 8	75.2	1.71	31	0.41	18.1	0.68	1.66
11/ 9	75.3	1.71	35	0.46	20.5	0.69	1.50
11/12	75.8	1.71	27	0.36	15.8	0.71	1.97
11/15	74.5	1.70	37	0.50	21.8	0.75	1.50
11/19	74.0	1.68	26	0.35	15.5	0.71	2.29
11/23	73.1	1.68	19	0.26	11.3	0.73	2.80
11/27	73.2	1.68	21	0.29	12.5	0.77	2.66
11/30	73.1	1.68	40	0.55	23.8	0.75	1.36
12/ 6	72.4	1.68	30	0.41	17.9	0.68	1.65
12/11	72.4	1.68	41	0.57	24.4	0.78	1.37
12/13	72.5	1.68	42	0.58	25.0	0.83	1.43
12/15	72.3	1.68	26	0.36	15.5	0.84	2.33
12/17	72.2	1.68	21	0.29	12.5
12/18	72.3	1.68	39	0.54	23.2
12/24	71.5	1.67	23	0.32	13.8
Average.....			31	0.41	18.1	0.72	1.89

TABLE 8.—*Insensible Perspiration*

Subject: C. B.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight			Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
			Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.		
6/13	91.5	2.02	22	0.24	10.9	0.73	3.04
6/14	91.6	2.02	28	0.35	13.9	0.71	2.03
6/15	91.8	2.02	31	0.34	15.3	0.73	2.15
6/18	91.5	2.02	29	0.32	14.4	0.80	2.50
6/19	91.1	2.01	26	0.28	12.9	0.77	2.75
6/20	90.7	2.01	32	0.35	15.9	0.73	2.09
6/21	91.0	2.01	18	0.20	9.0	0.68	3.40
6/22	89.7	2.01	36	0.40	17.9
6/23	89.5	2.01	27	0.30	13.4	0.73	2.43
6/25	89.4	2.01	35	0.39	17.4	0.81	2.08
6/26	89.9	2.01	36	0.40	17.9	0.75	1.88
6/27	90.1	2.01	31	0.34	15.4	0.81	2.38
6/28	90.0	2.01	34	0.38	16.9	0.83	2.19
6/29	89.6	2.00	24	0.27	12.0	0.85	3.15
7/ 2	88.6	1.99	35	0.40	17.6	0.78	1.95
7/ 3	88.7	1.99	39	0.44	19.6
7/ 4	88.1	1.99	35	0.40	17.6
7/ 5	87.6	1.98	33	0.43	19.2	0.85	1.98

TABLE 5.—*Weekly Averages of Daily Basal Heat Production*
Subject: C. B.; height, 168.9 cm.; age, 23 years; normal weight, 61.4 Kg.

Weeks	Weight			Heat Production						Pulse Rate
	Kg.	Daily Loss, Kg.	Per-centage Over Normal Weight	R. Q.	Calo-ries per Sq.M. per Hour	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	
1.....	94.5	−0.4	54.0	0.784	34.2	− 7.4	1,684	− 4.3	17.8	69
2.....	94.1	−0.1	53.3	0.801	33.6	− 9.2	1,649	− 6.1	17.4	64
3.....	93.1	−0.1	51.6	0.800	34.1	− 7.9	1,660	− 4.9	17.8	61
4.....	91.7	−0.3	49.3	0.763	33.6	− 9.3	1,628	− 6.0	17.8	60
5.....	90.7	−0.5	47.8	0.752	33.1	−10.3	1,598	− 7.3	17.8	58
6.....	89.7	+0.0	46.1	0.764	36.5	− 1.5	1,750	+ 1.8	19.6	58
7.....	87.8	−1.0	42.9	0.759	36.4	− 1.6	1,730	+ 1.7	19.8	61
8.....	87.0	+0.1	41.7	0.777	34.4	− 7.3	1,631	− 2.9	18.8	61
9.....	85.8	−0.4	39.8	0.771	34.9	− 5.7	1,646	− 1.9	19.2	64
10.....	85.3	−0.2	39.0	0.787	35.4	− 3.4	1,665	+ 0.6	19.5	57
11.....	85.4	+0.1	39.1	0.729	35.3	− 4.7	1,659	− 1.0	19.6	56
12.....	83.8	−0.4	36.6	0.762	34.8	− 6.1	1,596	− 2.3	19.0	60
13.....	82.9	−0.9	34.3	0.779	37.4	− 0.3	1,736	+ 5.6	21.1	64
14.....	81.3	−0.2	32.4	0.716	33.2	−10.3	1,536	− 6.0	18.9	56
15.....	81.0	−0.1	31.9	0.729	32.8	−11.3	1,520	− 6.7	18.8	56
16.....	80.8	+0.3	31.6	0.739	33.7	− 9.1	1,553	− 4.6	19.3	57
17.....	79.5	−0.3	29.4	0.728	36.1	− 2.4	1,647	+ 2.0	20.7	59
Average.....		−0.26	34.7	− 6.3	1,640	− 3.2	19.0	

TABLE 6.—*Weekly Averages of Daily Basal Heat Production*
Subject: H. M.; height, 159.4 cm.; age, 21 years; normal weight, 55.5 Kg.

Weeks	Weight			Heat Production						Pulse Rate
	Kg.	Daily Loss, Kg.	Per-centage Over Normal Weight	R. Q.	Calo-ries per Sq.M. per Hour	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	Percent- age of Devia- tion from Normal	Calo-ries per 24 Hours	
1.....	108.0	−0.2	94.6	0.716	35.7	−3.5	1,787	−5.3	16.6	67
2.....	106.8	−0.3	92.5	0.711	34.4	−6.9	1,712	−8.6	15.9	66
3.....	106.0	−0.2	91.0	0.732	34.4	−6.9	1,712	−7.9	16.2	63
4.....	104.7	−0.3	88.6	0.691	34.7	−7.5	1,701	−8.2	16.3	67
5.....	103.1	−0.3	85.8	0.724	35.0	−5.0	1,708	−7.1	16.6	67
Average.....		−0.26	34.8	−6.0	1,724	−7.4	16.3	

TABLE 7.—*Insensible Perspiration*
Subject E. S.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight			Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
			Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.		
9/27	80.1	1.75	27	0.34	15.4	0.78	2.30
9/28	79.6	1.75	30	0.38	17.2	0.81	2.13
9/30	80.1	1.75	38	0.48	21.7
10/11	79.7	1.75	27	0.34	15.4	0.72	2.12
10/ 2	79.7	1.75	25	0.31	14.3	0.79	2.55
10/ 4	79.6	1.75	39	0.49	22.3	0.80	1.64
10/ 5	79.5	1.75	24	0.30	13.7	0.71	2.37
10/ 7	79.2	1.75	43	0.54	24.6
10/ 8	79.4	1.75	37	0.47	21.2	0.70	1.49
10/10	78.3	1.73	32	0.41	18.5	0.69	1.68
10/11	78.4	1.73	38	0.49	22.0
10/12	78.3	1.73	42	0.54	24.3	0.72	1.33
10/13	78.4	1.73	22	0.28	12.7	0.68	2.43

COMMENT

The daily basal metabolism of all three subjects, as given in tables 1 to 3, fluctuated considerably, varying from 1,751 to 1,163 calories per twenty-four hours in E. S., from 1,876 to 1,392 calories in C. B. and from 1,880 to 1,616 calories in H. M. However, the weekly averages given in tables 4 to 6 show that as the weight of the subjects slowly decreased, there was also a gradual decrease in the heat production. This was less marked in C. B., who was more neurotic than the other two subjects. The high value of her last weekly average was due in part to the fact that she was restless and anxious to leave the hospital. On the basis of the averages of the first week and those of the next to the last week, her basal metabolism decreased from 1,684 to 1,553 calories per twenty-four hours as her body weight was reduced from 94.5 to 81 kilograms. In other words, a reduction of 16.7 per cent of body weight was accompanied by a decrease of 8.4 per cent in basal metabolism. The heat production of E. S. decreased steadily from a weekly average of 1,640 calories per twenty-four hours to that of 1,256, which was 17.5 per cent below her normal standard according to DuBois and 16 per cent below as compared with Benedict's standard. She was therefore given treatment with thyroid extract, first 1 and then 2 grains (0.06 and 0.13 Gm.) a day. In spite of the administration of thyroid extract, her basal metabolism decreased from 1,640 to 1,416 calories per twenty-four hours as her weight was reduced from 79.7 to 69.7 kilograms, using also the averages of the first week and those of the next to the last week of the experiment. The decrease in heat production in this subject exceeded that of her body weight. A reduction of weight of 14.3 per cent was followed by a lowering of 15.8 per cent in basal metabolism. Unfortunately, our best subject, H. M., who was calm and willing to cooperate, had to go home after taking part in the experiment for five weeks. In spite of the short duration of the experiment, she lost 4.9 kilograms, or 4.8 per cent of her initial weight. Her loss of weight was followed by a decrease of 4.6 per cent in basal metabolism, from a weekly average of 1,787 to that of 1,708 calories per twenty-four hours.

In the case of C. B., the diminution of body weight was accompanied by an increase in heat production when the latter was expressed as calories per kilogram per twenty-four hours. Thus, as the weight decreased from 95 to 79.7 kilograms, the basal metabolism increased from 17.4 to 21.4 calories per kilogram per twenty-four hours. No similar relationship was observed in the results of the other two subjects. Their heat production expressed as calories per kilogram of body weight fluctuated irrespective of the loss of weight. When the values of the weekly averages were used, the coefficient of correlation

TABLE 8.—*Insensible Perspiration—Continued*

Subject E. S.

Date	Body Weight, Kg.	Sq. Meter of Body Surface	Loss of Weight			Calories per Kg. per Hour	Ratio of Heat Production to Insensible Loss
			Per Hour Gm.	Per Kg. per Hour, Gm.	Per Sq. Meter per Hour, Gm.		
7/ 6	87.1	1.98	22	0.25	11.1
7/ 7	87.4	1.98	28	0.32	14.2	0.84	2.63
7/ 9	86.6	1.96	33	0.38	16.8	0.79	2.08
7/11	87.0	1.98	31	0.36	15.7	0.72	2.00
7/12	87.5	1.98	34	0.39	17.2	0.76	1.95
7/14	86.2	1.96	31	0.36	15.8
7/16	86.1	1.96	26	0.30	13.3
7/19	85.2	1.96	26	0.31	13.3	0.78	2.52
7/20	86.1	1.97	23	0.27	11.7	0.84	3.11
7/22	86.0	1.97	22	0.26	11.2
7/25	85.1	1.96	19	0.22	9.7	0.92	4.18
7/26	85.4	1.96	25	0.29	12.8	0.77	2.66
7/27	85.3	1.96	21	0.25	10.7	0.79	3.16
7/28	85.1	1.96	29	0.34	14.8	0.80	2.36
7/29	85.0	1.96	23	0.27	11.7
7/30	85.5	1.96	23	0.27	11.7	0.82	3.04
7/31	85.2	1.96	19	0.22	9.7	0.81	3.68
8/ 1	85.6	1.96	25	0.29	12.8
8/18	83.6	1.94	25	0.30	12.9	0.86	2.87
8/19	83.6	1.94	28	0.34	14.4
8/20	83.1	1.93	35	0.42	18.1	0.94	2.24
8/22	81.8	1.92	27	0.33	14.1	0.81	2.46
8/23	82.3	1.92	25	0.30	13.0
8/25	81.7	1.92	37	0.45	19.3
8/26	81.7	1.92	30	0.37	15.7
8/27	81.0	1.92	26	0.32	13.5	0.72	2.25
8/28	81.8	1.92	29	0.35	15.1	0.93	2.66
8/29	81.7	1.92	24	0.29	12.5
8/30	81.4	1.92	16	0.20	8.3
8/31	81.3	1.92	28	0.34	14.6	0.73	2.15
9/ 1	81.0	1.92	38	0.47	19.8	0.77	1.64
9/ 2	81.2	1.92	26	0.32	13.5
9/ 3	81.1	1.92	27	0.33	14.1
9/ 4	81.1	1.92	25	0.31	13.0	0.77	2.49
9/ 5	81.0	1.91	30	0.37	15.7	0.80	2.16
9/ 6	80.8	1.91	37	0.46	19.4	0.78	1.70
9/13	80.4	1.91	37	0.46	19.4	0.81	1.76
9/20	79.2	1.90	25	0.32	13.2	0.91	2.85
9/22	79.7	1.90	34	0.43	17.9	0.89	2.07
Average.....			29	0.33	14.5	0.80	2.92

TABLE 9.—*Ratio of Heat Production per Hour to Insensible Perspiration per Hour (Benedict-Root Table Recalculated)*

Insensible Perspiration, Gm.	Heat Produced per 24 Hours, Calories	Ratio of Heat Produced to Insensible Perspiration	Insensible Perspiration, Gm.	Heat Produced per 24 Hours, Calories	Ratio of Heat Produced to Insensible Perspiration
14	900	2.68	38	1,655	1.76
16	965	2.51	40	1,715	1.79
18	1,028	2.38	42	1,775	1.76
20	1,090	2.27	44	1,840	1.74
22	1,155	2.19	46	1,900	1.72
24	1,215	2.11	48	1,965	1.71
26	1,280	2.05	50	2,025	1.69
28	1,345	2.00	52	2,085	1.67
30	1,405	1.95	54	2,145	1.66
32	1,470	1.92	56	2,210	1.64
34	1,530	1.88	58	2,275	1.63
36	1,590	1.84			

The pulse rate of E. S. showed a tendency to vary with the basal heat production. The weekly averages ranged between 53 and 72. No relation between the pulse rate and the metabolism was found in the other two subjects. The pulse rate of C. B. varied from 54 to 72, with the majority lying between 55 and 65. The values for H. M. were exceptionally constant; the weekly averages ranged between 63 and 67.

During the experimental period the study of insensible perspiration was also conducted on two of the three subjects. The measurements were made during a ten hour period at night from 9:45 p. m. to 7:45 a. m., a platform scale being used, the so-called "silk scale" recommended by Benedict.⁴ Tables 7 and 8 show that the values varied widely in both subjects; in E. S. they ranged from 0.58 to 0.26, with an average of 0.41 Gm. per kilogram per hour. When computed on the basis of a square meter of body surface, they ran between 25 and 12.5; with an average of 18.1 Gm. per square meter per hour. The corresponding values for C. B. were 0.47 and 0.20, with an average of 0.33 Gm. per kilogram per hour and the values per square meter per hour were from 19.8 to 8.3, with an average of 14.5 Gm. The average insensible loss per hour of these two subjects was 31 and 29 Gm., which is in close agreement with the results reported by previous investigators on normal subjects. The average insensible perspiration per person reported by Benedict and Hendry⁵ from a study of a group of girls between the ages of 12 and 17 was found to be about 30 Gm. per hour, with the exception of two cases in which it was 38 and 45. In a later investigation⁶ made on two groups of girls, the same authors gave the average value as 33 Gm. per hour. In a study⁴ made on a woman weighing 60 kilograms, during the greater part of a year, Benedict and Root gave the average as 28.7 Gm. per hour. In the same report the authors also gave 24 Gm. per hour as the average insensible loss of a woman studied in a series of organized weighings with the platform scale.

In order to facilitate the comparison of basal heat production with the insensible loss, the ratio of the two was computed as is shown in tables 7 and 8. In each case, the basal metabolism was taken within an hour following the morning weighing. In E. S., the ratio varied from 2.8 to 1.33, with an average of 1.89. The corresponding values for C. B. were 4.18, 1.64 and 2.92. Since the latter subject is more

4. Benedict, F. G., and Root, H. F.: *Insensible Perspiration: Its Relation to Human Physiology and Pathology*, Arch. Int. Med. **38**:1 (July) 1926.

5. Benedict, F. G., and Hendry, M. F.: *The Energy Requirements of Girls from Twelve to Seventeen Years of Age*, Boston M. & S. J. **184**:217 (March 3) 1921.

6. Benedict, F. G.: *The Basal Metabolism of Young Girls*, Boston M. & S. J. **188**:127 (Feb. 1) 1923.

between the body weight in kilograms and the calories per kilogram per twenty-four hours was -0.71 for C. B., -0.33 and -0.25 for E. S. and H. M., respectively, showing a fair degree of inverse correlation in C. B. and only a slight correlation in the other two.

In comparing our results with normal standards using the actual weight of the patients, the basal metabolism of all three subjects was lower than either the Benedict or the DuBois standard. The average values were 9.3, 6.3 and 6.0 per cent below the DuBois standard or 7.7, 3.2 and 7.4 per cent below Benedict's. It is of interest to observe that with no exception in the case of C. B. and with a few exceptions in E. S., the values of heat production were closer to the Benedict standard than to the DuBois. On the other hand, the reverse was true in the case of H. M., who was far more obese than the other two. If the ideal weight of the subjects was used, the heat production of all three became higher than their standard. Thus, for instance, at the beginning of the experiment the heat production (using weekly averages) of E. S. was 25.6 per cent above the Benedict standard and at the end of the experiment, 15.3 per cent above. The corresponding values for C. B. and H. M. were 16.3, 13.8, 28.9 and 32.2, respectively. These values are in close agreement with those reported by Strang and Evans,² who pointed out that, using ideal weight, obese subjects invariably showed an increased basal metabolism which decreased with the reduction of body weight. Since the experimental diet was adequate in all food essentials except caloric value, which was lowered by reducing chiefly the fat content to a minimum, the decrease of body weight of these subjects must be due largely to the loss of adipose tissue. The reduction of their energy production is, therefore, probably the result of the biologic adaptation of the body to a lowered energy intake as was pointed out by Lusk.³

The influence of the reduction of body weight on the respiratory quotient varied with the subjects. There was a tendency toward a gradual decrease during the course of reducing weight in the case of C. B. The weekly averages of the first three weeks gave a value close to 0.8 which gradually decreased to a figure near 0.7 at the end of the experiment. The respiratory quotient of H. M. was unusually constant; the weekly averages varied from 0.691 to 0.732. In the case of E. S., the values fluctuated independently of body weight between 0.841 and 0.693.

2. Strang, J. M., and Evans, F. A.: The Energy Exchange in Obesity, *J. Clin. Investigation* **6**:277 (Oct.) 1928. Evans, F. A., and Strang, J. M.: A Departure from the Usual Methods in Treating Obesity, *Am. J. M. Sc.* **177**:339 (March) 1929.

3. Lusk, G.: The Physiological Effect of Undernutrition, *Physiol. Rev.* **1**:523 (Oct.) 1921.

THE ORIGIN OF UROBILINOGEN

A CLINICAL EXPERIMENT *

I. M. RABINOWITCH, M.D.

MONTREAL, CANADA

From time to time physiologists devise various experimental procedures to test their theories. Occasionally, however, one may meet with a clinical condition that corresponds to the ideal laboratory experiment for explaining a given phenomenon. The literature contains many such examples, and the case reported here is an additional demonstration. Its data are of interest particularly with regard to the origin of urobilinogen in the body.

Estimation of the urobilinogen content of urine has now been a routine in this laboratory for a number of years, particularly in the study of disorders of the blood and liver. All methods available have been tried, but from a quantitative point of view none has been found perfect. For practical purposes, however, the method described by Wallace and Diamond in 1925, has been found to be the most satisfactory and has been in use since it was first reported. As in all laboratory tests with a large routine and accumulation of data, anomalous results are met with. Provided technical errors have been eliminated, the interpretation of such results never fails to be of interest. They may alter the interpretation of future data and occasionally contribute to the knowledge of physiology.

Unless one is certain of the facts of an experiment and unless the results are definite, one should hesitate to publish data that might add to the confusion now existing with regard to the various functions of the liver. Mann put it very well when he stated that "the liver has served as the waste-basket of the body into which have been dumped numerous manuscripts of conjecture concerning obscure physiological and pathological phenomena and uncounted prescriptions." In the case to be reported, the experimental results were, however, sufficiently definite to warrant their publication.

It is not my purpose to review this subject in this brief report, as excellent reviews are now available in the literature. A few observations must, however, be made in order to separate theories from facts and also because they are essential for the interpretation of the data obtained.

* Submitted for publication, May 17, 1930.

* From the Department of Metabolism, the Montreal General Hospital.

excitable, a greater variation in the results would be expected. In comparison with the curve of the relationship between insensible perspiration per hour and the heat production per twenty-four hours constructed by Benedict and Root,⁴ our values do not agree closely with theirs. In the case of E. S., the insensible loss is usually higher than the predicted value, whereas the reverse is true of C. B.

Table 9 shows that, according to Benedict's prediction, the higher the basal metabolism is, the lower the ratio. Thus, by recomputing his table 4,⁴ as the basal metabolism ran from 900 to 2,272 calories per twenty-four hours, the ratio decreased from 2.68 to 1.63. The values of our two subjects failed to correspond with the foregoing prediction. E. S. had an average basal metabolism of 1,377 calories per twenty-four hours; the average ratio was 1.89, whereas C. B. had a higher basal, 1,640 calories per twenty-four hours, with a higher ratio of 2.92. We are unable to explain whether this discrepancy is due to the extra adipose tissues of our subjects or to some other biologic factors.

SUMMARY

1. A total of 190 metabolic tests were made during a period of reducing weight by diet in three obese women, one of whom had diabetes. In the latter a steady decrease in basal metabolism was observed until thyroid extract was administered. In the other two subjects, the decrease was less marked.

2. Per kilogram of body weight, the basal metabolism of one of the subjects, C. B., increased gradually with the loss of weight, but no such relationship was observed in the other two. The coefficient of correlation between the loss of body weight and the increase of heat production per kilogram per twenty-four hours showed a fair degree of inverse correlation, -0.71 in C. B. and only a very slight correlation in the other two, -0.33 and -0.25 , respectively.

3. A slight tendency toward the lowering of the respiratory quotient was observed in C. B., but not in the others.

4. In E. S., the pulse rate showed a tendency to decrease with the basal metabolism, but the values varied independently of the basal metabolism in the other two subjects.

5. Insensible perspiration of two of the subjects showed marked fluctuation. The average insensible loss was 31 Gm. per hour in E. S. and 29 Gm. in C. B. No definite relationship was found between insensible perspiration and basal metabolism in these two subjects.

The association of such large amounts of urobilinogen in the urine with normal quantities of bilirubin in the blood was never met with before in my experience. To exclude technical errors, the test was repeated on the afternoon of the same day; the results were the same.

In view of these observations and the prevalent conception of the physiology of bile pigment, I suggested that there was probably some extravascular accumulation of blood; and that this blood was being reduced to urobilinogen at its source. The latter suggestion appeared reasonable, since if the reduction was taking place in the intestines, it would imply that large amounts of bilirubin had to enter the circulation from the extravascular collection of blood. If this was the case, the plasma had to contain either free hemoglobin or excess bilirubin. There was no evidence of hemolysis, and the van den Bergh reaction was negative.

Though it is known that bilirubin may be reduced to urobilinogen by nonbacterial agents *in vitro* (sodium amalgam, etc.), as far as I could ascertain from the literature, bacterial reduction is the only type that has ever been reported in the body. It was therefore also suggested that this extravascular accumulation of blood was infected.

In making the foregoing suggestions, it was assumed that the van den Bergh reaction is specific for bilirubin and that the para-dimethyl-amido-benzaldehyde reagent used is specific for urobilinogen. As a matter of fact, the latter assumption is not correct, since the reaction is common to pyrrol groups. In view, however, of the large experience with this reagent, it may reasonably be assumed that the red color obtained when this reagent is added to urine is practically wholly due to urobilinogen.

On March 20, a laparotomy was performed and the preoperative diagnosis was proved to be partly correct. The condition was found to be a large ovarian cyst with torsion of the pedicle. The surface was very dark and obviously cyanotic. On opening the cyst it was found full of blood, a specimen of which was obtained for bacteriologic examination. The report from the pathologist showed that the blood was sterile.

That the mass of blood in the cyst was the source of the excessive amount of urobilinogen found in the urine appears obvious from the fact that in a specimen of urine obtained twelve hours after operation, that is, after the removal of the mass of extravascular blood, the quantity of urobilinogen was normal, namely, less than in 1:10 dilution. In this case, we therefore appear to have proof that urobilinogen can be formed not only outside of the intestinal tract but also in the absence of bacteria with reducing properties. An explanation for the development of the urobilinogen in the cyst is suggested.

Since the blood in the cyst was bathed with other body fluids, and since the latter contained oxygen in solution, one would hardly expect reduction of hemoglobin, in view of the marked avidity of the latter for oxygen. With the twisted pedicle, however, three conditions would immediately result, namely: (*a*) anoxemia, (*b*) accumulation of carbon dioxide and (*c*) because of the anoxemia, accumulation of lactic acid. According to hemoglobin dissociation curves, the increase of carbon dioxide tension and hydrogen ion concentration would lessen the avidity

There is general agreement that hemoglobin, bilirubin and urobilinogen are intimately related. Not only is there similarity between their chemical structures, but there is also experimental evidence: It has repeatedly been shown that urobilinogen may be produced, *in vitro*, by reduction of bilirubin with sodium amalgam or other reducing agents.

Whether bilirubin has its origin in the hemoglobin of the blood only or whether it is derived from other sources as well is still unsettled. No one, however, doubts that bilirubin can, and does, originate from hemoglobin. There may also be some doubt as to the relative importance of the different sites of bile formation (liver, bone-marrow, etc.). There appears, however, to be sufficient agreement that the liver can, and does, supply this function. The biliary passages are also the chief paths of elimination of these pigments, and by means of them the latter pass into the intestinal tract. With regard to the course of events beyond this stage, however, the subject is much more controversial.

There appears to be general agreement that in the intestine, because of the reducing properties of its flora, bilirubin is converted into urobilinogen. The urobilinogen may then follow one of three paths. It may be excreted with the feces or reabsorbed into the liver or into the circulation and eliminated in the urine. The amounts found in the urine are small, under normal conditions. Excessive quantities are found either in association with hepatitis or in conditions associated with excessive destruction of blood. Provided the liver is not exposed to organisms with reducing properties, it is generally accepted that extra-intestinal reduction of bilirubin to urobilinogen does not take place. Recently, Wallace and Diamond, following a review of this subject and some experimental work, again concluded that there is no extra-enterogenous formation of urobilinogen. The following case, however, is presented as evidence to the contrary. Though the experiment was clinical, the results, as I have stated, appear to have been so definite as to warrant their consideration. The data demonstrate not only the possibility of an extra-intestinal origin of urobilinogen, but also that the formation of this pigment from bilirubin may take place in the absence of its exposure to bacteria with reducing properties. The following are the relevant facts:

REPORT OF A CASE

A woman, aged 44, was admitted into the gynecological service of the Montreal General Hospital on March 16, 1930, with acute abdominal pain. The diagnosis was not definite, but the probabilities considered were (a) an ovarian cyst with torsion of the pedicle and (b) a malignant growth terminating in some form of abdominal crisis. As this report is essentially biochemical, no further observations are relevant with regard to the clinical aspects of the case. The laboratory observations of special interest here were as follows: urobilinogen was present in the urine in a dilution greater than 1:1,000; the van den Bergh reaction was negative.

of hemoglobin for oxygen; with progressive reduction, hemoglobin would be converted into bilirubin and then into urobilinogen.

The foregoing explanation is only a suggestion. The purpose of this report is to record a clinical experiment which appears to demonstrate that urobilinogen may not only be formed in the body outside of the intestinal tract, but also in the absence of bacteria as reducing agents.

Middleton and Thewlis,⁷ in a study of patients with catarrhal cholangitis, concluded that the protein factor was not essential for the production of hemoclastic shock. Feinblatt,⁸ in a study of eighty normal persons, found a consistent leukocytosis after the ingestion of milk. Of fifty patients with various diseases, he obtained a positive reaction in twenty-two.⁹ He concluded that a positive Widal reaction is indicative of faulty hepatic proteopexic function, and that the test is not a measure of the quantitative gross lesion.¹⁰

Brown¹¹ accepted the test as probably yielding information respecting special functions of the liver, but he drew no conclusions from his own observations on patients with questionable disease of the liver.

Sabin, Cunningham, Doan and Kindwall¹² showed that regardless of digestion, the leukocytes had a normal physiologic rhythm which was approximately hourly. At every hourly period the leukocyte count reached a peak which was followed by a depression of varying depth. At times the fall in the number of leukocytes reached 50 per cent of the preceding peak. This rhythmic curve ascended through the day to the afternoon, so that the high counts of the afternoon doubled the low counts of the morning.

Mention has already been made of other workers who have recognized a normal variation in the leukocytes.¹³ Shaw,¹⁴ working independently, was able to confirm the work of Sabin and her co-workers, and showed also that there was a diurnal variation in the leukocytes. Doan and Zervas¹⁵ showed that comparable leukocyte

7. Middleton, W. S., and Thewlis, Ethel: The Leukocytic Phase of Haemoclastic Shock, *J. Lab. & Clin. Med.* **10**:462, 1924 and 1925.

8. Feinblatt, Henry M.: Alimentary Leukocytosis in Eighty Normal Men: A Study in Reference to the Crise Hémoclasique of Widal, *J. A. M. A.* **80**:613 (March 3) 1923.

9. Feinblatt, Henry M.: Alimentary Leukocytosis in Various Pathologic Conditions: A Further Study in Reference to the Crise Hémoclasique of Widal, *Arch. Int. Med.* **33**:210 (Feb.) 1924.

10. Feinblatt (footnotes 8 and 9).

11. Brown, Thomas: Notes on Hemoclastic Shock as a Test of Liver Function, *Ann. Clin. Med.* **1**:89 (Sept.) 1922.

12. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: The Normal Rhythm of the White Blood Cells, *Bull. Johns Hopkins Hosp.* **37**:14, 1925.

13. Shaw (footnote 2). Mauriac and Cabouat (footnote 3). Servantie, Panzat and Monod (footnote 4).

14. Shaw, A. F. B.: The Diurnal Tides of the Leucocytes of Man, *J. Path. & Bact.* **33**:1, 1927.

15. Doan, C. A., and Zervas, Leon G.: The Rhythmic Range of the White Blood Cells in Human Pathological Leucopenic and Leucocytic States with a Study of Thirty-Two Human Bone Marrows, *J. Exper. Med.* **46**:511, 1927.

is made, and immediately 200 cc. of milk is given by mouth. White blood cell counts are repeated every twenty minutes for two hours. In the presence of liver dysfunction, leukopenia develops, usually within the first hour, the maximum of which is reached in the first twenty to forty minutes. At the end of ninety minutes, the count returns to the control level or goes above it. When the liver is intact, the counts do not fall below the initial count, and a leukocytosis may follow (digestive leukocytosis).

The authors obtained a positive reaction in thirty-eight of thirty-nine patients with disease of the liver. The test gave negative results in all of eleven normal persons, in nine of whom leukocytosis appeared. The test gave negative results in other pathologic conditions in which the liver was intact.

REVIEW OF THE LITERATURE

The literature, which is largely European, is divided in its criticism of the work. The value of the test and its theoretical basis are both disputed. Shaw² applied the test to seven patients with disease of the liver, and to twenty-three normal persons. He controlled his results by making serial counts while the patient was at rest, and by giving substances other than milk—distilled water, casein and butter fat. His conclusions were: 1. The leukocyte count under normal conditions fluctuates considerably, but at times it is in equilibrium. 2. There is no digestion leukocytosis or "digestion leukopenia," and the results recorded as such in the literature on hemoclasia are simply an expression of the phase of the normal curve at the time the test is done.

The author quoted Mauriac and Cabouat,³ Servantie, Panzat and Monod⁴ and Kobryner⁵ to support his observations of variations in the leukocytes in normal subjects at rest.

Storm van Leeuwen, Bien and Varekamp⁶ obtained a fall in leukocytes in normal and in asthmatic persons within two minutes after the ingestion of a meal. They showed that the curves varied in the same subjects when the counts were repeated. They concluded that the leukocyte curve does not give evidence of a "crise hémoclasique."

2. Shaw, A. F. Bernard: A Study of the Haemoclastic Crisis Test for Liver Function, With Special Reference to the Leucocytic Changes, *Brit. M. J.* **1**:914 (May 16) 1925.

3. Mauriac, P., and Cabouat, P.: *Paris méd.* **11**:407, 1921.

4. Servantie; Panzat and Monod: *J. de méd. de Bordeaux* **12**:360, 1921.

5. Kobryner, A.: *Compt. rend. Soc. de biol.* **90**:1475, 1924.

6. Storm van Leeuwen, W.; Bien, Z., and Varekamp, H.: On Alimentary Leucocytosis in Its Relation to the Crise Hémoclasique of Widal, *J. Exper. Med.* **36**:414, 1922.

Bergh) was increased in all patients. The bromsulphalein test showed a retention in twelve of the seventeen, the output of urinary urobilinogen was increased over the normal in nine, and the levulose tolerance was impaired in six. In fifteen patients the tests were positive in combinations, no two of which were always together. In only two patients (13 and 15) was the van den Bergh reaction alone positive. On two patients with cardiac disease who had congestive heart failure (13 and 17) and on one patient (14) who had acute catarrhal jaundice, the study was repeated after there was marked clinical improvement. The results of

Results of Correlation Between Widal's Leukocyte Test and That of Sabin, in a Series of Twenty Patients with Disease of the Liver

Case	Diagnosis	Jaundice	Liver, Cm. from Xiphoid	Bromsulphalein, per Cent	Serum Bilirubin, Mg. per Cent	Urobilinogen, Dilu. + 1 in.:-	Levulose Tolerance			
							Fast-ing	30	60	120
1	Carcinoma of liver.....	+	20	15	3.8	160	69	84	82	100
2	Cardiac.....	0	8	5	0.92	128	92	120	135	133
3	Carcinoma of stomach....	0	7	5	0.51	40	77	98	100	96
4	Acute jaundice.....	++	4	35	12.5	20	93	119	137	105
5	Cardiac.....	0	0	0	<0.5	4	78	92	106	81
6	Cardiac.....	0	10	15	1.1	32	82	96	103	105
7	Parkinsonian syndrome...	0	0	0	<0.5	8	100	125	125	100
8	Cardiac.....	+	13	5	4.3	64	108	125	130	127
9	Cardiac.....	0	10	5	0.17	128	100	114	117	110
10	Cardiac.....	0	16	5	0.63	15	108	125	137	125
11	Acute jaundice.....	++	0	0	3.0	80	62	66	80	91
12	Cirrhosis of liver.....	0	18	0	0.94	32	97	116	146	144
13a	Cardiac.....	0	15	0	1.8	16	78	82	95	105
13b	0	8	0	<0.5	2	72	82	90	100
14a	Acute jaundice.....	++	12	20	10.1	20	77	88	109	83
14b	0	0	0	<0.5	40	101	105	118	100
15	Abscess of liver.....	0	8	0	1.1	4	100	100	102	109
16	Cardiac.....	0	11	15	0.94	16	70	95	100	102
17a	Cardiac.....	0	12	0	0.64	8	100	135	181	210
17b	0	5	0	<0.5	4	117	122	128	114
18	Jaundice following the use of arsphenamine.....	++++	7	10	9.0	512	137	150	155	166
19	Cardiac.....	0	0	0	<0.5	4	80	95	94	81
20	Acute jaundice.....	++	4	5	3.3	16	83	80	117	79

the second series of tests are given in the table in spaces 13-b, 17-b and 14-b. In each of these instances, a test previously positive became negative. In the case of 14-b, a single specimen of urine gave a positive reaction for urobilinogen in a dilution of 1:40, despite the fact that numerous specimens both at the height of the disease and subsequently were always negative when dilutions of more than 1:20 were used. The latter three patients served as controls, both for themselves and for the entire group.

On the basis of these tests and the observations made clinically and at autopsy, it was assumed that all of the patients except the ones used as controls had abnormalities of the liver, either structural or functional or both. It was felt, therefore, that this was a group of patients on whom the value of Widal's leukocyte test for liver function could be studied.

rhythms occur in many types of disease. Smith and McDowell¹⁶ found the rhythm unaffected during menstruation, mild fatigue and moderate exercise.

If this rhythmic variation is accepted as a normal physiologic process of the leukocytes, then Widal's leukocyte test for liver function becomes untenable. To be of any value, the control counts must extend over a period sufficiently long to portray the physiologic rhythm of the leukocytes, and to interpret a positive reaction, either the entire rhythmic curve of the leukocytes must be depressed, or, if the interpretation is to depend on the results in the sixty minutes succeeding the ingestion of milk, the depression must exceed the physiologic depression. It seemed, therefore, that additional information to the subject could be made if in a series of patients with disease of the liver, Widal's leukocyte test for liver dysfunction was correlated with the work of Sabin and her collaborators.

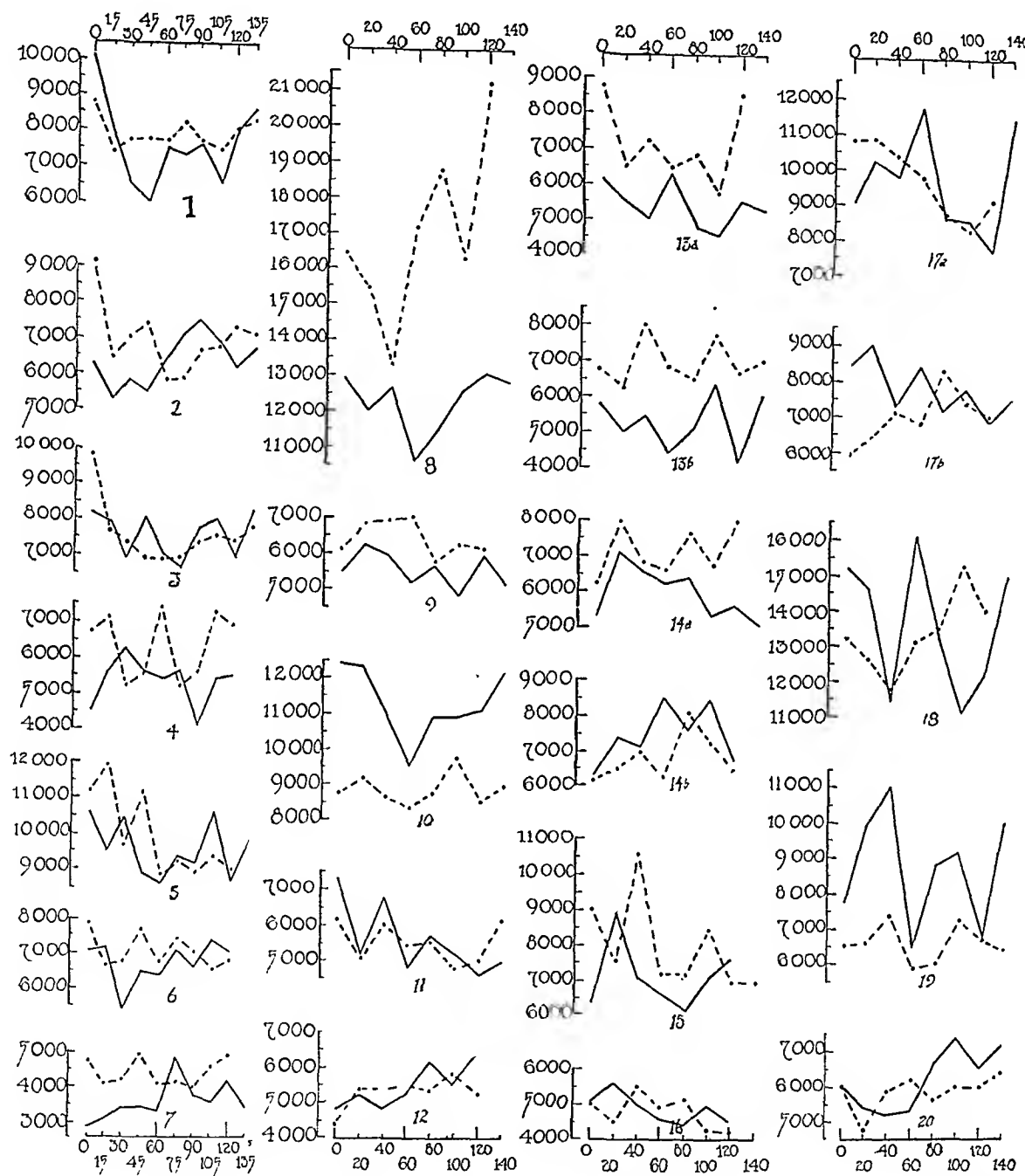
REPORT OF STUDY

The study was made on twenty hospital patients. Ten had heart disease; in eight of these there was congestive failure with enlarged livers, and in two the hearts were well compensated and served as controls. Four were patients with acute catarrhal jaundice; one patient showed extensive primary carcinoma of the liver, later proved by autopsy; one was a patient with carcinoma of the stomach who probably had extensive liver metastasis; one patient had jaundice following the administration of arsphenamine; one patient had an amebic abscess of the liver which was drained by repeated aspiration with apparent cure; one patient had cirrhosis of the liver; and one patient with a parkinsonian syndrome was used as a control. Evidence of disease of the liver was determined by the clinical study and by the results of four tests for liver function carried out on each patient. These were: the levulose tolerance test, the bromsulphalein test, a daily determination of the urinary urobilinogen according to the technic of Wallace and Diamond¹⁷ and quantitative determinations of serum bilirubin (van den Bergh). The results of these tests are shown in the accompanying table.

All of the patients studied showed some form of abnormality of the liver except those who served as controls (5, 7 and 19). In only one patient (11) were we unable to palpate the liver. In each patient, at least one of the four tests for liver function showed a deviation from the normal. The serum bilirubin (the quantitative test of van den

16. Smith, Christiana; and McDowell, Anna Mary: Normal Rhythm of White Blood Cells in Women, *Arch. Int. Med.* **43**:68 (Jan.) 1929.

17. Wallace, George B., and Diamond, Joseph S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch. Int. Med.* **35**:698 (June) 1925.



Curves showing total white blood cell counts for twenty subjects. The abscissas represent time in minutes; the ordinates represent the number of leukocytes. In each case the value of the ordinates is given to the left of the curve. The broken line is the control curve; the solid line, the test curve.

The method was to make counts of the total white blood cells at either fifteen or twenty minute intervals for a period of two hours or more. Two series of counts, a control and test series, were done on each patient. Usually these counts were done on consecutive mornings; in a few instances, they were done on consecutive afternoons. When the counts were done in the morning, the patient omitted his breakfast. In those instances in which the study was made in the afternoon, the patient had been without food or drink for at least five hours. The control series of counts was done while the patient was fasting; the test series was done under the same conditions, except that the patient was given 200 cc. of milk by mouth immediately after blood was withdrawn for the first or key count. The same pipet and counting chamber were used for all observations, and an automatic lancet was used to puncture the skin. The blood was drawn from the finger tips, and a different finger was used for each count. Duplicate counts were done and the average of the two taken. All of the counts were done by the same observer.

The counts are plotted in curves in the accompanying chart. Inspection of the chart shows at once that extensive fluctuations occur in both the control and the test curves. They are not long enough to show any definite rhythm, but in a general way they show depressions and ascents rather than a tendency toward a horizontal straight line.

A study of all the control curves shows that there is at least one period in each curve, except that of patient 12, in which there is a peak and a subsequent fall. Each of these depressions in the curves might have been interpreted as a positive Widal reaction had a test meal been given immediately following the peak count. The control curves show, therefore, that Widal's leukocyte test as it is described by the authors cannot be used to determine liver function.

The second phase of the problem was to determine whether the test meal depressed the entire rhythmic curve and whether such depression could be interpreted as a positive Widal reaction. In only four of twenty-three test curves (1, 11, 16, 17-*b*) might such a deduction be made. On the other hand, in as many of the control series of curves (2, 3, 5, 17-*a*) the same downward tendency existed. There is no evidence, therefore, that the meal depressed the entire curve during the period studied. If such a depression exists beyond the two hour period, this fact does not lend support to the criteria set down by Widal and his collaborators that after ninety minutes the white blood count comes back to the control level or goes above it.

The third phase of the study was to determine whether the ingestion of the test meal was followed by an immediate fall in the number of white blood cells which was greater than the greatest fall that occurred anywhere in the control curves. It is clear that the initial fall succeeding

SPHENOPALATINE PHENOMENA

PRESENT STATUS OF KNOWLEDGE *

HIRAM BYRD, M.D.

IN COLLABORATION WITH

WALLACE BYRD, A.B.

DETROIT

Our object in this paper is to bring together the more important observations that have accumulated in the literature on the sphenopalatine ganglion during the past twenty-five years and the more important observations that have been made during eight years of original work on this subject. The original work includes more than 2,000 cases and more than 10,000 instances, counting multiples and repetitions, of remote dysfunctions¹ being arrested by anesthetizing the sphenopalatine ganglions. This should provide a working guide that will bring the student of the subject to the front lines of advance without unnecessary delay.

Anesthetization of the sphenopalatine ganglions and the injection of alcohol into them have one feature in common: They render the ganglions impervious to the passage of nerve currents. An injection may be considered the equivalent of an anesthetization lasting several months instead of several hours, and so the associate phenomena need not be discussed separately.

* Submitted for publication, May 25, 1930.

* From the Jefferson Clinic and Diagnostic Hospital.

1. The term dysfunction is here used as synonymous with Sir Arthur Lovatt Evans' phrase, "a state of disease:" "A state of disease is never a thing in itself, but is always a quantitative change in some physiological process, an increase or diminution of something that was there to begin with." (Address of the President, Section 1, Physiology, British Association for the Advancement of Science, 1928.) Dysfunction, then, is a quantitative change whereby a function passes beyond physiologic limits, and arrest of dysfunction is a quantitative return of the process to within physiologic limits. Any less comprehensive term would be insufficient to include the wide range of phenomena observed. In many of these cases the arrest of a malady leaves no detectible trace of a pathologic process; it is as if no such process had existed; in others a residuum of the process remains, but soon disappears, as if the process had been arrested. In still other cases the pathologic process seems to be arrested for the time, but tends to recur at varying intervals. The most accurate term applicable to these varying phases would seem to be "dysfunction."

the test meal must be compared, not with the initial fall of the control curve, but with the greatest fall in that curve. Such comparison shows that in only seven of the twenty-three instances (1, 6, 10, 11, 13-b, 18, 20) did the depression succeeding the test meal exceed the greatest depression in the control. The number is less than one third of the total number of curves and is what might be anticipated if the test meal does not affect the number of leukocytes. If comparison is made between the greatest depression in test curve, regardless of its relationship to the antecedent test meal, with the greatest depression in the control curve, then in thirteen sets of curves (1, 6, 10, 11, 13-b, 18, 20, 4, 7, 14-a, 17-a, 17-b, 19) the greatest depression occurs in the test curve; in the other ten sets, the greatest depression appears in the control curves. The numbers are sufficiently close to indicate that the control and test curves are similar.

Further evidence that the two curves are similar is evinced when one considers the number of depressions that might be interpreted as positive Widal reactions were test meals given at the preceding peak count. Such consideration shows that there are a total of thirty-two depressions in all of the control curves and thirty in the test curves.

SUMMARY AND CONCLUSION

Serial counts of the total number of leukocytes were made every fifteen or twenty minutes for two hours on seventeen patients who showed evidences of liver dysfunction. These determinations were made according to the technic outlined by Widal for determining such dysfunction. A control series of counts was made under the same conditions, except that the test meal was omitted. Marked fluctuations occurred in the total number of leukocytes from period to period in both series of curves. There was no evidence that the ingestion of milk had any effect on the number of white blood cells in the peripheral circulation during a two hour period. From this study no evidence can be adduced that Widal's leukocyte test for hemoclastic crisis is a test for liver function.

most frequently noted. Sluder³ said: "That the pain of all eye lesions may be stopped by cocain to the nasal ganglion . . . is a fact which has been repeatedly observed." This statement does not seem overdrawn. There are few, if any, pains in the eyes not represented in the list, and they are relievable in a majority of cases. Of the various pains and other dysfunctions of the eye and periocular structures that have been thus arrested we may mention more specifically: the pain of iritis, observed by Sluder,³ Byrd⁴ and Ryerson;⁵ the pain of keratitis, observed by Sluder,³ Byrd⁴ and Ryerson;⁵ the pain of interstitial keratitis associated with syphilis, observed by Byrd;⁴ the pain of conjunctivitis, observed by Sluder,³ Byrd⁴ and Ryerson;⁵ the pain of optic neuritis from methyl alcohol poisoning, observed by Byrd;⁴ the pain of traumatic ulcer of the cornea, observed by Sluder³ and Byrd;⁶ blepharospasm, observed by Sluder;³ functional hyperesthesia of the ciliary muscle, observed by Sluder;³ pain in the eye associated with errors of refraction, observed by Byrd;⁴ photophobia, observed by Sluder,³ Byrd⁴ and Ryerson;⁵ excessive lacrimation, observed by Sluder,³ Byrd⁴ and Ryerson;⁵ intra-ocular tension and pain of glaucoma, observed by Sluder,³ Miller,⁷ Byrd⁸ and Ryerson;⁵ the pain of phlyctenula, observed by Sluder³ and Byrd,⁴ and the pain of chalazion, observed by Byrd.⁴ Dysfunctions of and about the ear include: the pain of otitis media, observed by Sluder³ and Byrd;⁴ chronic otorrhea, observed by Byrd;⁴ otalgia, observed by Sluder,³ Clerf,⁹ Gugenheim,¹⁰ Hansel,¹¹ Byrd⁴ and Lillie;¹² mastoidalgia, observed by Sluder,³ Lillie,¹² Cook¹³ and Byrd;⁴ itching of the external auditory canal, observed by Byrd⁴ and Ruskin;¹⁴ tinnitus aurium,

4. Unpublished cases of the authors.

5. Ryerson, F. L.: Personal communication to the authors.

6. Byrd, H.: Pathological Impulses or Currents, *M. J. & Rec.* **121**:141 (Feb.) 1925.

7. Miller, H. E, quoted by Sluder (footnote 3, p. 99).

8. Byrd, H.: Influence of Nasal Ganglion in Treatment of Glaucoma, *Arch. Ophth.* **56**:162 (March) 1927.

9. Clerf, L. H.: Control, Through the Nasal Ganglion, of Earache of Laryngeal Origin, *J. A. M. A.* **82**:630 (Feb. 23) 1924.

10. Gugenheim, L. K., quoted by Sluder (footnote 3, p. 273).

11. Hansel, F. K.: Otolgia from Abscess of the Tongue Controlled by Cocainization of the Nasal Ganglion, *Arch. Otolaryng.* **7**:165 (Feb.) 1928.

12. Lillie, H. W., quoted by Sluder (footnote 3, p. 273).

13. Cook, J. D.: Symptomatology of a Case of Sphenopalatine Ganglion Neurosis, *J. Missouri M. A.* **21**:319 (Sept.) 1924.

14. Ruskin, S. L.: The Nasal Ganglion in Relation to Itching of the Auditory Canal and Tinnitus Aurium, *Arch. Otolaryng.* **2**:269 (Sept.) 1925; Herpes Zoster Oticus Relieved by Sphenopalatine Ganglion Treatment, *Laryngoscope* **35**:301 (April) 1925.

Anesthetization of the sphenopalatine ganglion is accomplished by topical application of 2 minims (0.12 cc.) of 50 per cent butyn to the lateral wall of the nasopharynx posterior to the tip of the middle turbinate.²

"A pinch of cotton is wound upon the tip of the applicator into a smooth, compact spindle about five millimeters in diameter at the center. This is dipped into the adrenalin and squeezed dry between the forefinger and thumb so as to flatten it in the same plane with the bent handle. At the same time the tip is bent to an angle of about thirty degrees in this plane. Two drops of butyn are added, and the applicator is now ready to be placed.

"Standing on the right side of the patient, with the left forearm resting upon the patient's head and the left forefinger slightly raising the tip of the nose, the operator introduces the applicator, coaxing it along the floor of the nose or wherever its passage is found to be easiest, to a depth of about two and three-quarter inches, when it will be felt to come into the open space of the nasopharynx. The curved tip is now rotated outward to an angle of about forty-five degrees, when it makes contact with the pharyngeal wall. It is left in this position for about five minutes, close watch being kept during this time to see that contact with the wall is continuous, when anesthesia of the sphenopalatine ganglion should be complete.

"Caution: During this process close observation should be made of an untried patient, and should any pallor, nausea, or other untoward symptom supervene, the test should be discontinued."

The act of anesthetization is unavoidably preceded by some nasal irritation incident to the introduction of an applicator into the nasopharynx. A number of phenomena, such as lacrimation, itching of the roof of the mouth, twitching of the alae of the nose, coughing, sneezing, the temporary augmentation of remote dysfunctions and sometimes relief from remote dysfunctions, are observed during this brief period of nasal irritation. Such phenomena, however, will not be considered here, as this article is limited to phenomena appearing when the ganglions become impervious to the passage of nerve currents, which occurs from two to five minutes after anesthetization.

The first recorded instance of a remote dysfunction arrested by anesthetization of the sphenopalatine ganglion occurred in a case of headache relieved by Sluder³ in 1903. Subsequently such arrest of dysfunctions has been observed in the neck, trunk and extremities. It is in dysfunctions about the eyes, however, that these phenomena are

2. The authors' technic for anesthetization of the sphenopalatine ganglion (quoted from J. Michigan M. Soc. 29:294 [April] 1930) is as follows: "Armamentarium: an applicator, absorbent cotton, adrenalin, and butyn. The applicator is of aluminum, and slender, with about two centimeters of the tip subjected to heat for pliability. The cotton should be of long fiber; the adrenalin, 1/1000; and the butyn a 50 per cent aqueous solution.

3. Sluder, Greenfield: Nasal Neurology, Headaches and Eye Disorders, St. Louis, C. V. Mosby Company, 1927.

Respiratory dysfunctions arrested by anesthetizing the sphenopalatine ganglions include: hay-fever, observed by Sluder,³ Payne,²⁸ Gundrum²⁹ and Byrd;³⁰ sneezing, observed by Byrd;⁴ dyspnea, observed by Byrd;⁴ hiccup, observed by Hansel,³¹ Rehfeldt,³² Costen³³ and Byrd;⁴ cough, observed by Byrd,⁴ and asthma, observed by Sluder,³ Gundrum³⁴ and Byrd.³⁵ Passing to diseases of the lower trunk, we may note: chronic inguinal distress following herniotomy, observed by Byrd;³⁶ diarrhea, observed by Sluder;³ renal colic, observed by Chester;²⁵ gallstone colic, observed by Chester;²⁵ frequent micturition, observed by Sluder;³ pain of cystitis, observed by Sibley;³⁷ ovaritis, observed by Byrd⁴ and Warren;²⁴ dysmenorrhea, observed by Byrd,⁴ Warren²⁴ and Gundrum,²² and the vomiting of pregnancy, observed by Warren.²⁴ Another group of dysfunctions arrested includes: chronic sore spots at the lower border of the ribs, the coccyx, the cervical lymphatics, the breast and the larynx, observed by Byrd,³⁸ and the pain of cancer of the uterus, breast and larynx and just below the left clavicle, observed by Byrd.³⁸ Rheumatoid dysfunctions arrested by anesthetizing the sphenopalatine ganglion include: sciatica, observed by Byrd³⁹ and Ruskin,¹⁷ neuritis, observed by Byrd;⁴ pleurisy, observed by Byrd;⁴ lumbago, observed by Sluder,³ Byrd⁴⁰ and Saunders;⁴¹ the pain of arthritis, observed by Byrd;⁴² the pain of gout, observed by Byrd;⁴ the pain of bunions,

28. Payne, R. J.: Treatment of Nasal Ganglion in Hay Fever, *J. Missouri M. A.* **21**:257 (Aug.) 1924.

29. Gundrum, L. K.: Nasal Ganglion Neuroses, *California & West. Med.* **24**:204 (Feb.) 1926.

30. Byrd, H.: Hay Fever, Its Control Through Efferent Interception, *Ann. Int. Med.* **3**:850 (Feb.) 1930; Hay Fever, Its Surgical Conquest, *Laryngoscope*, to be published.

31. Hansel, F. K., quoted by Sluder (footnote 3, p. 275).

32. Rehfeldt, C. S.: Control of Intractable Singultus (Hiccough) Through the Nasal Ganglion, *Laryngoscope* **35**:354 (May) 1925.

33. Costen, J. B.: Persistent Hiccough: Control by Cocainization of the Nasal Ganglion, *Ann. Otol. Rhin. & Laryng.* **37**:860 (Sept.) 1928.

34. Gundrum, L. K.: Asthma and Eczema Controlled Through the Nasal Ganglion, *Ann. Clin. Med.* **4**:573 (Jan.) 1926.

35. Byrd, Hiram; and Byrd, Wallace: The Clinic as a Field for Biologic Research, *Clin. Med. & Surg.* **37**:95 (Feb.) 1930. Byrd, H.: The Sphenopalatine Test, *J. Michigan M. Soc.* **29**:294 (April) 1930.

36. Byrd (footnote 35, second reference).

37. Sibley, C. P.: Personal communication to the authors.

38. Byrd, H.: Pathological Currents and Cancer, *J. Cancer Research* **3**:13 (Oct.-Dec.) 1926; footnote 4.

39. Byrd (footnotes 4 and 35).

40. Byrd, H.: Blocking Off Remote Pain at the Nasal Ganglia, *M. J. & Rec.* **120**:126 (suppl.) (Oct. 15) 1924; footnote 36.

41. Saunders, D. U.: Personal communication to the authors.

42. Byrd (footnote 4; footnote 40, first reference).

observed by Byrd⁴ and Ruskin;¹⁵ progressive deafness, observed by Byrd;⁴ sense of fulness of the ear, observed by Ruskin;¹⁴ sense of fulness of the ear of allergic origin, observed by Byrd;⁴ pain in the external auditory canal associated with fungus infection, observed by Byrd;⁴ ear cough, observed by Byrd,⁴ and herpes zoster oticus, observed by Ruskin.¹⁶ Dysfunctions about the nose and throat that have been arrested include: the pain of maxillary, frontal and ethmoid sinusitis, observed by Sluder³ and Byrd;⁴ rhinorrhea, observed by Sluder³ and Byrd;⁴ acne rosacea, observed by Sluder³ and Byrd;⁴ toothache in the upper jaw, observed by Sluder³ and Byrd;⁴ parageusia, observed by Sluder³ and Ruskin;¹⁷ itching of the roof of the mouth, observed by Byrd;⁴ unilateral burning sensation in the roof of the mouth, observed by Ruskin;¹⁷ pain associated with Vincent's angina, observed by Byrd;⁴ glossodynia, observed by Sluder,³ Dean¹⁸ and Engman;¹⁹ the pain of follicular tonsillitis, observed by Byrd;⁴ the pain of tonsillar diphtheria, observed by Byrd;⁴ the pain of septic sore throat, observed by Byrd;⁴ the pain of peritonsillar abscess, observed by Byrd⁴ and Hoople;²⁰ postoperative pain, after tonsillectomy, observed by Byrd;⁴ pain of tuberculous laryngitis, observed by Gundrum;²¹ external cricoidynia, observed by Sluder,³ and spasm of the esophagus, observed by Sluder.³ As we pass from dysfunctions about the head to those of the trunk and extremities, we may mention: migraine, observed by Sluder³ and Gundrum;²² vertigo, observed by Byrd,⁴ and nausea, observed by Byrd.⁴ Among dysfunctions of the circulatory system that have been arrested to date are: angina pectoris, observed by Heitger²³ and Byrd;⁴ hypertension, observed by Byrd,⁴ Warren²⁴ and Ryerson;⁵ Buerger's disease, observed by Chester;²⁵ tachycardia, observed by Goldschmidt-Osmund²⁶ and Byrd,⁴ and cardiospasm, observed by Ruskin.²⁷

15. Ruskin (footnote 14, first reference).

16. Ruskin (footnote 14, second reference).

17. Ruskin, S. L.: Contributions to Study of the Sphenopalatine Ganglion, *Laryngoscope* **35**:87 (Feb.) 1925.

18. Dean, L. W.: The Control of Glossodynia, *South. M. J.* **15**:856 (Oct.) 1922.

19. Engman, M. F., quoted by Sluder (footnote 3, p. 273).

20. Hoople, G. D.: A New Method of Anesthesia for Opening Peritonsillar Abscess, *Laryngoscope* **36**:577 (Aug.) 1926.

21. Gundrum, L. K.: Pain from Tuberculous Laryngitis Relieved by Cocainization of the Nasal Ganglion, *J. A. M. A.* **83**:998 (Sept. 27) 1924.

22. Gundrum, L. K.: Migraine Controlled Through the Nasal Ganglion, *Arch. Otolaryng.* **8**:564 (Nov.) 1928.

23. Heitger, J. D., quoted by Sluder (footnote 3, p. 289).

24. Warren, E. W.: Personal communication to the authors.

25. Chester, John L.: Personal communication to the authors.

26. Goldschmidt-Osmund, Bruno, quoted by Sluder (footnote 3, p. 101).

27. Ruskin, S. L., quoted by Sluder (footnote 3, p. 279).

hunger, sometimes associated with periods of blurred vision, which she called "blind spells." She had been much worse for the past three weeks, and had been without sleep for the past forty-eight hours. At this time she had severe pain about the left cheek and eye, and both swelling and tenderness in the thyroid region. The left sphenopalatine ganglion was anesthetized. Within five minutes the patient was free from pain, relaxed and sleepy. When seen after four hours of sleep, she was still comfortable. The swelling and tenderness of the thyroid area had somewhat abated. She slept soundly that night, and when seen the next morning was only moderately hungry, free from pain and feeling generally well. She was kept in bed on a light diet for ten days without treatment. During this interval, the cervical swelling and tenderness gradually reappeared, together with the former symptoms—pain, tremor, hunger and tachycardia. With the patient under general anesthesia, 95 per cent alcohol was injected into the left sphenopalatine ganglion. On the following day, the patient resumed her normal activities, free from all symptoms. At the end of nine months there had been no recurrence.

Before entering into a discussion of these phenomena, it seems pertinent to indicate what is meant by a dysfunction being relieved. We do not consider a dysfunction relieved unless the relief is complete and occurs within five minutes from the placement of the anesthetic. Cases in which the patient experiences merely improvement, even though quite distinct, are considered negative, because in our experience such cases tend to show less and less reaction to subsequent treatments.

In this connection it should be noted that the relief is generically different from that obtained by the administration of drugs. This difference appears in the rapidity with which relief is obtained, in its completeness and particularly in the fact that it is not accompanied by any unnatural sensations, nor followed by any physiologic after-effects that we can detect, but leaves the patient feeling as if the dysfunction had never existed.

For mechanical reasons, however, certain types of patients, although relieved from active symptoms, continue to present a residuum of dysfunction until physiologic repairs can be effected. For instance, when postoperative pain is relieved by anesthetization of the sphenopalatine ganglion, the wound is still sensitive to pressure. In arthritis, when hyperplasia has occurred some remaining soreness in the joint is to be expected; in asthma, though the dyspnea is immediately relieved, the excess secretions in the lungs cause a residuum of irritation that may last for several hours.

The presence of a residuum of sensitiveness raises a most significant question: Is this relief brought about by cutting the sensory path from the affected locus to the brain, i. e., by intercepting the message of pain, or must it be ascribed to some other cause? Consideration of this question, however, will be deferred until the end of the article.

observed by Byrd,⁴ and, perhaps of a similar nature, pain associated with flatfoot, observed by Byrd.⁴ The motor dysfunctions arrested include: writer's cramp, observed by Sluder;³ professional cramp, observed by Sluder;³ motor weakness of the forearm, observed by Sluder,³ and chorea of the arm and the leg, observed by Byrd.⁴³ Other dysfunctions arrested by anesthetizing the sphenopalatine ganglion are: the pain and soreness of a surgical and infected hand, observed by Byrd;⁶ pruritus vulvae, observed by Byrd,⁴ and eczema, observed by Gundrum.³⁴ In addition, a great variety of less sharply defined dysfunctions have been arrested. These include neuralgic and rheumatoid pains throughout the head, neck, trunk and extremities, observed by Sluder,³ Byrd⁴² and others. A conception of the wide range of dysfunctions arrested by anesthetizing the sphenopalatine ganglion is given

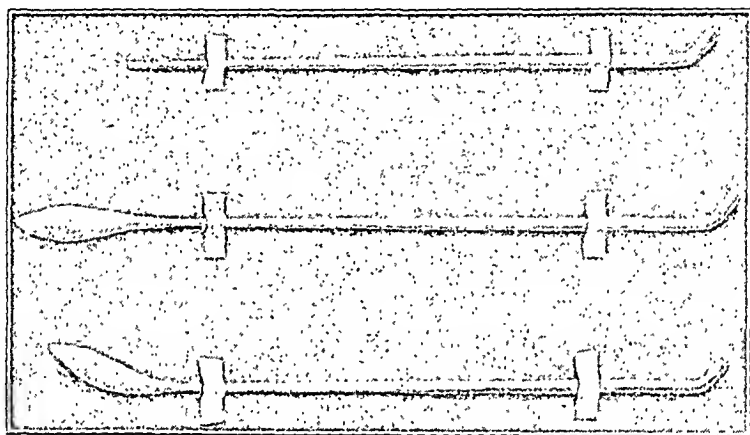


Fig. 1.—The upper figure is an aluminum applicator with a curved handle and a softened tip. The center figure shows a pledget of cotton wound on the applicator in spindle form, and the lower figure shows the pledget of cotton properly flattened and curved for introduction.

in Dock's masterly paper read before the American Medical Association in July, 1929.⁴⁴

It may be noted that the dysfunctions arrested involve the following categories: sensory, motor, secretory, respiratory and circulatory. In the light of this one would expect the endocrine dysfunctions to be similarly arrested. The following case, seen with Dr. H. J. Jensen, of Tampa, Fla., is offered for whatever significance the reader wishes to attach to it.

Mrs. T., when first seen, was suffering from pain in the head and eyes, with a general tremor. The pulse rate was 180 per minute. She complained of having had disagreeable symptoms for four years, with periods of excessive

43. Byrd, H.: Chorea, *Arch. Otolaryng.* 7:257 (March) 1928.

44. Dock, George: Sluder's Nasal Ganglion Syndrome and Its Relation to Internal Medicine, *J. A. M. A.* 93:750 (Sept. 7) 1929.

grinding brought on temporarily by anesthetization of the sphenopalatine ganglion. It is reassuring, however, to note that the percentage of cases in which dysfunctions are augmented or initiated is small. In a series of more than 10,000 anesthetizations ⁴ less than 20 such instances have been observed.

PROPORTIONS

From the considerable list of dysfunctions arrested by anesthetizing the sphenopalatine ganglion it is not to be inferred that the symptoms are thus arrestible in every case, but merely that an arrestible one occurs here and there. Of two indistinguishable cases of sciatica, for example, it will be found that one can be arrested by anesthetizing the sphenopalatine ganglion, while the other cannot. The same is true of angina pectoris, chorea, asthma, and so on, throughout the whole category.

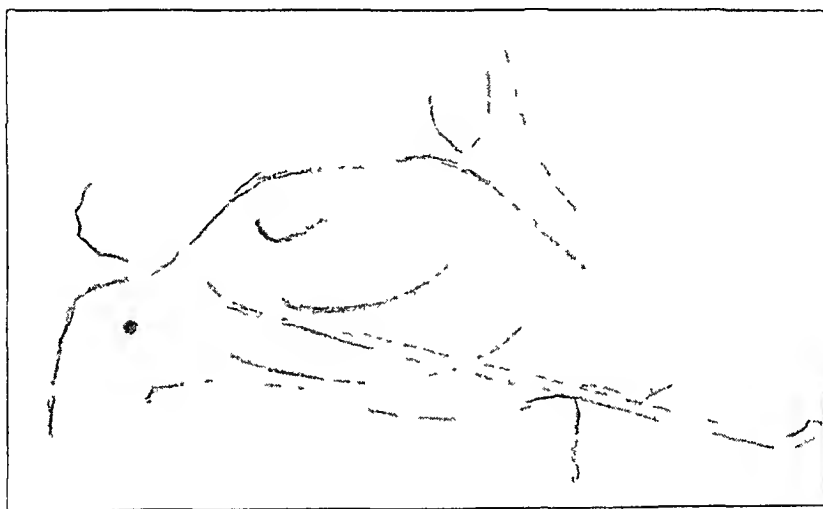


Fig. 2.—Side view of the lateral wall of the nasal chamber, with applicator in place.

In painful afflictions of the eye a considerable majority of cases may be expected to be relieved, and in dysfunctions about the maxillary sinus, the frontal sinus and the tonsillar fossae perhaps a majority may be relieved. In dysfunctions of the ear, such as otitis media, earache and progressive deafness, the proportion is somewhat less, while for the most part, dysfunctions below the neck show a still smaller proportion of positive reactions. A notable exception is lumbago, which appears to be relieved in an ample majority of cases. Dr. Saunders,⁴¹ at Eloise Infirmary where anesthetization of the sphenopalatine ganglion for lumbago is now a routine procedure, is of the opinion that relief may be expected in fully three fourths of the cases. In sciatica, however, our experience indicates that the proportion is about 1:4 or 1:5. In hypertension the percentage seems to be a little higher and in asthma a little lower.

REGIONS

On the basis of sphenopalatine phenomena, three anatomic regions are observed: two lateral halves above the neck and the rest of the body. Above the neck dysfunctions are arrestible with somewhat greater frequency than below, and always from the same side. In general, it may be said that dysfunctions below the neck are arrestible from the ganglion of the same side, the opposite side or neither. Certain specific dysfunctions, however, appear to be more frequently arrested from one side than from the other. Sciatica and the rheumatoid dysfunctions, for example, tend to be arrestible, if at all, by anesthetization of the left sphenopalatine ganglion, while asthma is seldom if ever arrested except from the right. Angina pectoris, as far as we know, has been arrested only from the left.

DURATION

In a case of chorea ⁴³ it was found that anesthetization of the sphenopalatine ganglion uniformly kept the malady in abeyance for a period of four hours. From this and similar experiences it is inferred that four hours is the life of the anesthetic when used in this connection.

The four hour interval has given us an important dividing line: Patients in whom the relief lasts four hours or more tend to recover under repeated anesthetization, while those in whom the relief lasts less than four hours tend to become less and less amenable to this type of treatment.

DIVERSITY OF EFFECTS

From what has been said it is apparent that in the presence of almost any dysfunction, near or remote, the sphenopalatine ganglion may be anesthetized with some hope of relief. In some cases it succeeds, and in others it fails; however, it should be noted that in a few cases it more than fails, actually augmenting or even initiating a dysfunction.

Sluder ³ was the first to observe the augmentation of a dysfunction by anesthetization of the sphenopalatine ganglion, as shown in deep temporal headache. Our experience has confirmed this observation in a number of cases, but has not extended it to other dysfunctions. Sluder cited Pollock ⁴⁵ as having initiated sciatica by injection of the sphenopalatine ganglions. Our experience does not include the initiation of any rheumatoid dysfunctions, either by injection or by anesthetization. We have observed fainting, nausea, palpitation, dyspnea,⁴ and an urticaria-like eruption as rare manifestations that could not be explained as drug hypersensitiveness, since they were not precipitated by similar application on the opposite side. Dr. George Dock ⁴⁶ has observed an uncontrollable impulse to press the teeth together without

45. Pollock, H. L., quoted by Sluder (footnote 3, p. 276).

46. Dock, George: Personal communication to the authors.

glion; after three such anesthetizations, he has been free from the malady for four months. On the other hand, in the next case that appeared, outwardly indistinguishable from the first, the patient did not obtain the slightest relief.

FUTILITY OF FREQUENT REINJECTION

References in the literature to reinjection of the sphenopalatine ganglions with alcohol at brief intervals call for some comment. It seems to be a generally accepted fact that the injection of alcohol into a nerve defunctionizes it for a number of months, roughly a year. We have no reason for supposing that the sphenopalatine ganglion is any exception to this general rule. Hence, to make reinjections before the effect of the previous injection is gone would be like reanesthetizing while anesthetization is still in effect. Our experience seems to confirm this.

THE SPHENOPALATINE TEST

Since the effect of anesthetization and injection may be considered the same except in duration, anesthetization affords a ready test to determine whether the injection of alcohol is indicated. Injections should never be made into the ganglion except on the basis of the sphenopalatine test;³⁶ that is, injection should be made only when it has been shown on a number of occasions that anesthetization relieves the dysfunction immediately (from two to five minutes), completely and for a period of four hours or more.

The sphenopalatine test is applicable in the determination of the advisability, not only of injections, but of proposed reinjections. A positive sphenopalatine test within a few days or weeks after an injection has been made into the ganglion shows that the injection missed its mark, while a positive test ten months or a year after an injection shows that the effect of the injection has passed away. In either case reinjection is permissible.

One should never be in haste to make injections, but should apply the sphenopalatine test from six to a dozen times beforehand. In most cases, after a series of anesthetizations it will be found that the dysfunction has either been relieved indefinitely or has ceased to be amenable to this type of procedure. Few injections are really indicated.

THE PATH OF PAIN NOT OBSTRUCTED

It is demonstrable that when pain is relieved by anesthetization of the sphenopalatine ganglion the locus of distress is not anesthetized. The cornea that is relieved from the pain of a corneal ulcer is still just as sensitive to a wisp of cotton as the cornea of the opposite eye. The pain associated with an inflamed and bulging ear-drum may be relieved,

THERAPEUTIC APPLICATION

When a sphenopalatine ganglion is anesthetized and a dysfunction arrested, the first question that presents itself is whether the relief will be permanent. In some cases it will. In a large majority of cases of lumbago, for example, whenever the sphenopalatine reaction is positive, the lumbago never returns. In noninfectious iritis ("cold settled in the eye") anesthetization of the ganglion of the same side relieves all the discomfort, while a drop of epinephrine relieves the congestion so that in a period of five minutes the eye is brought to what seems to be a normal state. In a great majority of such cases there is no recurrence of the symptoms.

All cases are not so readily amenable, however. Sciatica, for example, may be relieved and later return, requiring two, three, four or more anesthetizations before there is final cessation of the disturbance. In some instances a dysfunction may continue to return even after repeated anesthetizations, each of which arrests it for four hours or more. For these, the injection of alcohol into the strategic ganglion is indicated. Thus the patient with chorea, whose case was cited, was always relieved for four hours by anesthetization of the left sphenopalatine ganglion, and was finally given permanent relief by the injection of alcohol.

It should also be noted that in some cases relief for four hours or more is obtained for a time, but after a number of days or weeks some change occurs, whereupon the ganglion suddenly ceases to be strategic, and no relief can be obtained by its anesthetization. This phenomenon is especially frequent in cases of asthma. For example, in the case ⁴ of Mrs. G., who had had asthma for the past year, the right sphenopalatine ganglion was anesthetized during a desperate attack. The relief was complete within five minutes and lasted twelve hours. Subsequent attacks during the ensuing two weeks were similarly arrested, the respite lasting uniformly for four hours or more. The question in mind was whether it was not time to inject alcohol into the ganglion. This question was soon answered in the negative, however, by an attack in which anesthetizing the ganglion failed to give any degree of relief. Henceforth any therapeutic approach to the case via the sphenopalatine ganglion was futile.

In contrast with this, Mrs. R. had been a sufferer from asthma for more than forty years when it was found that anesthetizing the right sphenopalatine ganglion during an attack arrested it. Four or five other anesthetizations whenever the asthma recurred during the next few months effected relief which has lasted for five years.

Similarly, in a recent case of sciatica (H3260), the patient was relieved in midattack by anesthetization of the left sphenopalatine gan-

regions in which dysfunctions may be potentially relieved would pass into a state of anesthesia whenever the ganglion was anesthetized; since these regions include all the major ones of the body, such anesthesia would be widespread. Moreover, if this were true, the injection of alcohol into the ganglion would make this widespread anesthesia persist for a number of months. Such effects are not in accordance with clinical experience.

Whatever may be the mechanism by which pain is relieved when the sphenopalatine ganglion is anesthetized, it is not anesthesia of the erstwhile locus of distress, i. e., not obstruction of the sensory path.

CONCLUSION

Dysfunctions numbering more than threescore have been relieved by anesthetization of the sphenopalatine ganglions, including afflictions as intractable as progressive deafness, as painful as migraine and iritis and as grave as glaucoma and angina pectoris. A therapeutic measure which results in the mastery of a serious disease, such as diphtheria or diabetes, is hailed as a victory. Anesthetization of the sphenopalatine ganglion does not give relief in all cases of any one malady, but may be confidently expected to do so in at least one fifth of all cases of the several serious afflictions mentioned, which is equal to relief in all cases of one of them. Besides this, anesthetization of the sphenopalatine ganglion gives relief in a certain percentage of cases of more than threescore other dysfunctions, ranging from sciatica and pruritus to chorea and hypertension.

Furthermore, while anesthetization of the sphenopalatine ganglion has not in itself accomplished the conquest of any one disease, it has led directly to the therapeutic mastery of hay-fever, vasomotor rhinitis and polypoid degeneration.

A procedure which gives relief in even a moderate proportion of cases of more than threescore dysfunctions and in a majority of cases of certain others must have a sum total of therapeutic usefulness of the first magnitude, especially as it displaces no existing device in our armamentarium.

We believe that anesthetization of the sphenopalatine ganglion should be a routine procedure in every one of the dysfunctions enumerated, not only as a preliminary test, but as a therapeutic measure in cases that show a positive reaction. The sum total of its usefulness is such that it should command the attention of every one who engages in the practice of medicine.

but paracentesis immediately afterward is none the less painful.⁴⁷ The pain of sciatica, arthritis, gout, bunions or even of an acute infection⁴⁸ may be relieved, but sensitiveness in the region of distress is not detectably blunted.

Hople²⁰ mentioned having anesthetized the sphenopalatine ganglion in the presence of a peritonsillar abscess, thus producing anesthesia of the tonsillar area so that the abscess could be opened. Although we entertain the greatest respect for this observer, our own observations lead us to doubt whether a critical examination would reveal any anesthesia in the tonsillar region incident to anesthetizing the sphenopalatine ganglion. This doubt is based on several considerations:

1. We have many times anesthetized the ganglion in the presence of a normal tonsil and have endeavored without success to demonstrate even a slight trace of anesthesia in the tonsillar area.⁴⁹

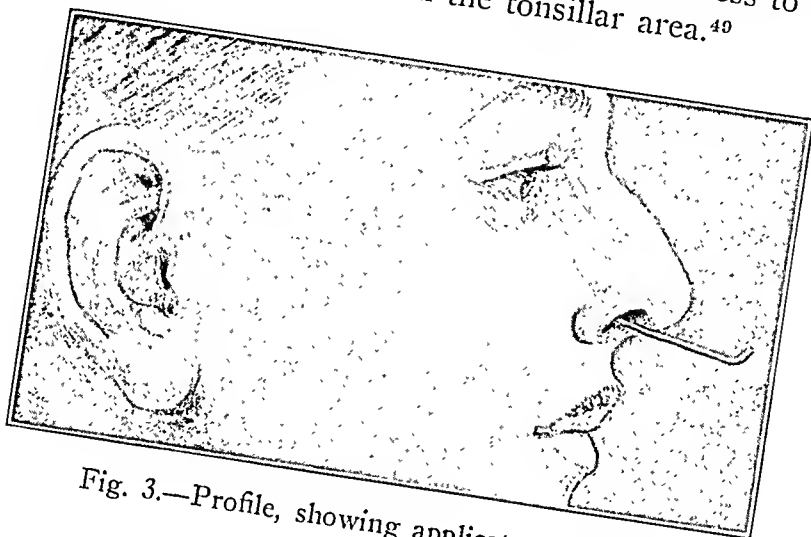


Fig. 3.—Profile, showing applicator in place.

2. We have repeatedly opened peritonsillar abscesses with relatively little pain after anesthetization of the sphenopalatine ganglion, whereas before anesthetization such a procedure would have been impossible. Yet in such cases we have been unable to demonstrate any anesthesia in the affected tonsil as compared with the tonsil of the opposite side. What did happen was that the pain and soreness incident to the abscess were relieved by anesthetization of the sphenopalatine ganglion of the same side, the area being thus converted from one of great distress to one of relative comfort. Under these circumstances the pain when a peritonsillar abscess is opened apparently is not intolerable.

3. If it were true that anesthetizing the sphenopalatine ganglion gave relief through producing anesthesia of the affected region, all

47. Sluder (footnote 3). Byrd (footnote 4).

48. Byrd (footnote 4). Pollock (footnote 45).

49. Whenever the ganglion has been anesthetized for any purpose, the following simple test for tonsillar anesthesia is suggested: With an applicator carrying a wisp of cotton compare the two tonsils for sensitiveness.

regions in which dysfunctions may be potentially relieved would pass into a state of anesthesia whenever the ganglion was anesthetized; since these regions include all the major ones of the body, such anesthesia would be widespread. Moreover, if this were true, the injection of alcohol into the ganglion would make this widespread anesthesia persist for a number of months. Such effects are not in accordance with clinical experience.

Whatever may be the mechanism by which pain is relieved when the sphenopalatine ganglion is anesthetized, it is not anesthesia of the erstwhile locus of distress, i. e., not obstruction of the sensory path.

CONCLUSION

Dysfunctions numbering more than threescore have been relieved by anesthetization of the sphenopalatine ganglions, including afflictions as intractable as progressive deafness, as painful as migraine and iritis and as grave as glaucoma and angina pectoris. A therapeutic measure which results in the mastery of a serious disease, such as diphtheria or diabetes, is hailed as a victory. Anesthetization of the sphenopalatine

cases of more than threescore dysfunctions and in many of certain others must have a sum total of therapeutic usefulness of the first magnitude, especially as it displaces no existing device in our armamentarium.

We believe that anesthetization of the sphenopalatine ganglion should be a routine procedure in every one of the dysfunctions enumerated, not only as a preliminary test, but as a therapeutic measure in cases that show a positive reaction. The sum total of its usefulness is such that it should command the attention of every one who engages in the practice of medicine.

SERUM TREATMENT FOR CHRONIC ULCERATIVE COLITIS *

J. ARNOLD BARGEN, M.D.

EDWARD C. ROSENOW, M.D.

AND

GEORGE F. C. FASTING, M.D.

ROCHESTER, MINN.

One of the most severe, debilitating infections is chronic ulcerative colitis of the type in which we¹ have shown a diplostreptococcus to have etiologic significance. Its onset may be insidious, beginning with the passage of blood, mucus and pus, mixed with the stool, at times associated with abdominal cramps and tenesmus, but not necessarily with marked increase in the number of passages. It may also start as a severe, fulminating illness, with many bloody, rectal discharges mixed with pus, with gruelling cramps, fever (figs. 1 and 2), and marked prostration.

CORRECTION

In this issue the headings at the tops of some of the pages of the article by Bargaen et al. and of that by Wolferth and Margolies have been accidentally transposed.

Submitted for publication, April 15, 1930.

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1930.

* From the Division of Medicine and the Division of Experimental Bacteriology, the Mayo Foundation.

1. Bargaen, J. A.: Changing Conceptions of Chronic Ulcerative Colitis, J. A. M. A. **91**:1176 (Oct. 20) 1928; Chronic Ulcerative Colitis: A Review of Investigation on Etiology, Arch. Int. Med. **45**:559 (April) 1930.

2. Buie, L. A.: Chronic Ulcerative Colitis, J. A. M. A. **47**:1271 (Oct. 16) 1926. Carman, R. D., and Moore, A. B.: The Roentgenologic Findings in Ulcerative Colitis, Am. J. Roentgenol. **16**:17 (July) 1926.

3. Bargaen, J. A., and Weber, H. M.: Regional Migratory Chronic Ulcerative Colitis, Surg. Gynec. Obst. **50**:964 (June) 1930.

4. Bargaen, J. A.: Specific Serum Treatment in Chronic Ulcerative Colitis, Arch. Int. Med. **43**:50 (Jan.) 1929.

found the use of whole immune horse serum unsatisfactory because of the frequent severe "serum sickness" which results from its administration in doses sufficient to produce results. That the course of the disease has been favorably influenced in many of the very sick patients,

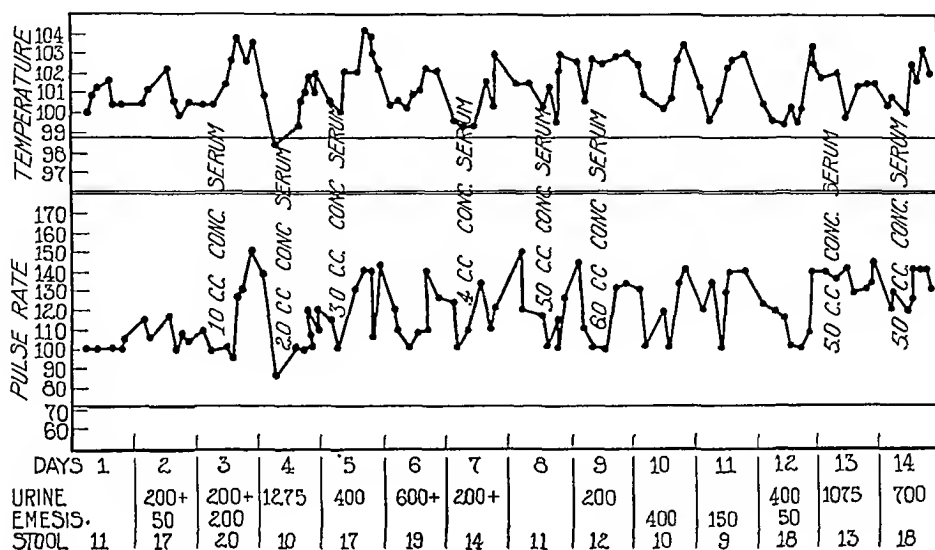


Fig. 1.—Data concerning the condition of the patient represented by case 29 (tabulation) during her first two weeks in the hospital.

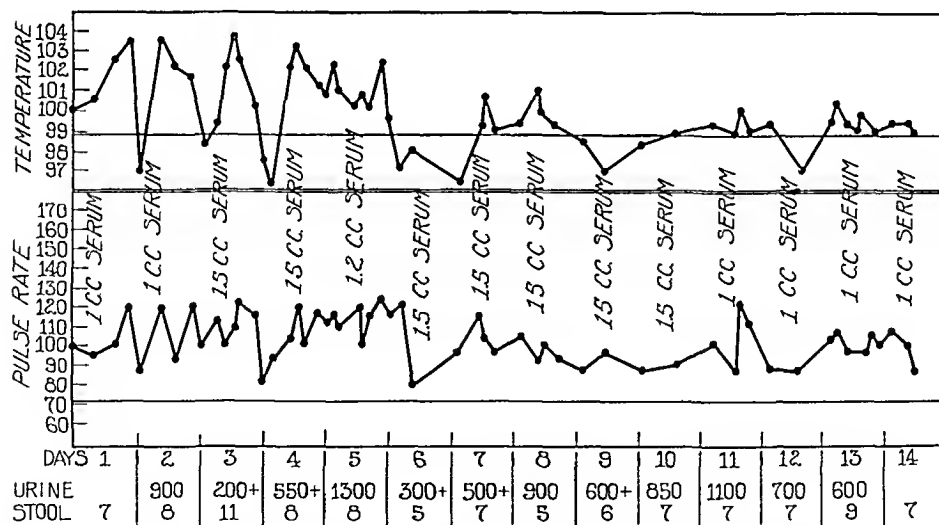


Fig. 2.—Data concerning the condition of the patient represented by case 9 (tabulation), during her first two weeks in the hospital. The fever subsided when treatment was begun.

has been shown in a sufficiently large number of cases to make it urgent that the factor which causes the distressing "serum sickness" be reduced, or, if possible, entirely removed.

SERUM TREATMENT FOR CHRONIC ULCERATIVE COLITIS *

J. ARNOLD BARGEN, M.D.

EDWARD C. ROSENOW, M.D.

AND

GEORGE F. C. FASTING, M.D.

ROCHESTER, MINN.

One of the most severe, debilitating infections is chronic ulcerative colitis of the type in which we¹ have shown a diplostreptococcus to have etiologic significance. Its onset may be insidious, beginning with the passage of blood, mucus and pus, mixed with the stool, at times associated with abdominal cramps and tenesmus, but not necessarily with marked increase in the number of passages. It may also start as a severe, fulminating illness, with many bloody, rectal discharges mixed with pus, with gruelling cramps, fever (figs. 1 and 2), and marked prostration, somewhat in the manner of other severe infectious diseases. Between the two extremes are all gradations of seriousness in symptoms, which depend, in large measure, on the extent of involvement of the large intestine. The disease affects various portions, or all, of the large intestine but, except later in the severer cases, rarely attacks the terminal portion of the ileum.² Clinical, proctoscopic and roentgenologic evidence supports the assumption that the disease usually starts in the rectum. However, any portion of the large intestine may be affected.³

We have reported previously on the use of specific vaccines and serum as part of the treatment for this disease.⁴ The type of case most suitable for treatment by specific vaccines has been described. We have

* Submitted for publication, April 15, 1930.

* Read before the American Gastro-Enterological Association, Atlantic City, N. J., May 5, 1930.

* From the Division of Medicine and the Division of Experimental Bacteriology, the Mayo Foundation.

1. Bargaen, J. A.: Changing Conceptions of Chronic Ulcerative Colitis, *J. A. M. A.* **91**:1176 (Oct. 20) 1928; Chronic Ulcerative Colitis: A Review of Investigation on Etiology, *Arch. Int. Med.* **45**:559 (April) 1930.

2. Buie, L. A.: Chronic Ulcerative Colitis, *J. A. M. A.* **47**:1271 (Oct. 16) 1926. Carman, R. D., and Moore, A. B.: The Roentgenologic Findings in Ulcerative Colitis, *Am. J. Roentgenol.* **16**:17 (July) 1926.

3. Bargaen, J. A., and Weber, H. M.: Regional Migratory Chronic Ulcerative Colitis, *Surg. Gynec. Obst.* **50**:964 (June) 1930.

4. Bargaen, J. A.: Specific Serum Treatment in Chronic Ulcerative Colitis, *Arch. Int. Med.* **43**:50 (Jan.) 1929.

centrated material is diluted with water and brought to a hydrogen ion concentration of 7.8. The refined serum used for injection into patients is made to contain about 2 mg. of nitrogen in each cubic centimeter.

The strikingly successful results that this material has yielded and the absence of the former distressing systemic serum-effect have led us to extend its use from the severe cases of acute illness to the more chronic and more resistant cases. In the strictest sense there is no such condition as "acute" ulcerative colitis of this bacterial type. The dis-



Fig. 3.—Roentgenogram after the administration of a barium enema, obtained in case 9 (tabulation). Extensive deformity and irregular mucosal edges corresponding to the deeper ulcerations are evident.

tinction is merely a matter of degree of chronicity. This fact must be kept in mind in the treatment in these cases.

The antibody euglobulin solution has now been administered in approximately 200 cases of chronic ulcerative colitis. It is given deeply in the muscles. We feel that the earlier cases have been under observation sufficiently long to justify an expression of opinion as to the value

The serum has been prepared by injecting into horses, increasing doses of freshly isolated strains of the diplostreptococcus, and by using many of these strains after they have been preserved, during the period of immunization, in dense suspensions in a mixture of two parts of glycerin and one part of a solution of sodium chloride, 25 per cent. This method has been shown to preserve specificity of the streptococci for a long time. Intravenous injections were given on three successive days each week, beginning with 5,000,000,000 dead organisms. The dosage was gradually increased to 2,000,000,000,000 organisms. After immunization had been continued for from two to four months, live organisms were given. Bleedings were made from seven to ten days after the last previous injection, at intervals of from three to six weeks, depending on the condition of the animal. The bleedings were made in a sterile manner from the jugular vein. The serum was drawn from the clotted blood after the clot had been squeezed with tinned weights for from twenty-four to forty-eight hours, and had been proved sterile by making aerobic, partial-tension and anaerobic cultures, as well as by inoculation of animals. The serum was used after immunization had been continued for months and not until it had a high agglutinating and precipitating titer, as well as protective power against the experimental disease in rabbits.

Because the administration of this serum caused a decidedly favorable influence on the course of severe, fulminating cases of chronic ulcerative colitis, it seemed highly important that some simple method be devised of preparing its effective portion so that its administration could be continued over a considerable period. Felton⁵ has prepared a satisfactory product for use in pneumonia by a simple method of concentration of antipneumococcus serum. Following his suggestions, one of us (G. F. C. F.⁶) has prepared an antibody solution from whole serum of chronic ulcerative colitis by methods similar, in some ways, to Felton's, but more satisfactory in many essentials for our purpose.

One part of immune serum is diluted with ten parts of acidulated 5 per cent ether-water. The reaction is kept at a hydrogen ion concentration near 7. At a hydrogen ion concentration of 7, immune chronic ulcerative colitis serum yields a modified euglobulin containing essential antibodies. This euglobulin settles out in a few hours, is collected, and is dissolved in a mixture of glycerin and salt. The concentration of glycerin and salt is sufficiently high to act as a preservative. The con-

5. Felton, L. D.: A Study of the Isolation and Concentration of the Specific Antibodies of Antipneumococcus Sera, Boston M. & S. J. **90**:819 (May 15) 1924.

6. Fasting, G. F. C.: On the Concentration of Antistreptococcus Serum, J. Infect. Dis. **45**:360 (Nov.) 1929.

Summary of Serum Treatment in Fifty Cases

Case	Age and Sex	Duration of Disease, Years	Extent of Disease, Roentgenologically	Grade by Procto-scope	Hemo-globin, per Cent	Culture		Primary Improvement, per Cent	Comment
						Rectal Mucosa	Blood		
1	36F	2	From anus to middle of descending colon	2	43	+	..	100	Recurrence; treated with vaccine; quick recovery; free from symptoms at last report
2	42F	1.33	From anus to hepatic flexure.....	3	33	+	..	100	Had remained free from symptoms at last report
3	25F	5	Entire colon and terminal ileum.....	3	64	+	+	100	Complicated by erythema nodosum; had remained free from symptoms at last report
4	34F	2	Entire colon and terminal ileum.....	3	43	+	..	75	Complicated by polyps; originally 20 bloody stools each day; at last report 5 without blood
5	28M	6	From anus to hepatic flexure.....	2	49	+	..	100	Recurrence after one year; prompt control by vaccine; free from symptoms at last report
6	60M	0.5	2	78	+	..	100	Had remained free from symptoms at last report
7	17M	3	Entire colon and terminal ileum.....	3	58	+	..	Slight	Originally severe hemorrhages; at last report bleeding stopped, but little change in number of stools
8	63M	0.5	3	80	+	..	100	Had remained free from symptoms at last report
9	22F	3	Entire colon.....	3	..	+	..	100	Complicated by perirectal abscess; recurrence in nine months; treated again by antibody solution; almost free from symptoms at last report
10	22F	2	Entire colon.....	2	40	+	..	100	Had remained free from symptoms at last report
11	25F	2	Entire colon.....	2	40	+	..	100	Complicated by endocarditis; recurrence; controlled by vaccine; free from symptoms at last report
12	29F	1	From anus to middle of descending colon	2	70	+	..	100	Had remained free from symptoms at last report
13	34F	1	1	70	+	..	100	Had remained free from symptoms at last report
14	18F	3	Entire colon and terminal ileum.....	2	54	+	..	100	Had remained free from symptoms at last report
15	42F	6	Entire colon.....	2	68	+	..	100	Had remained free from symptoms at last report
16	16F	3	Entire colon.....	2	57	+	..	100	Had remained free from symptoms at last report
17	18M	2	Entire colon.....	2	61	+	..	100	Had remained free from symptoms at last report
18	57M	0.25	Entire colon.....	2	30	+	..	100	Had remained free from symptoms at last report
19	31M	3.5	Entire colon.....	2	65	+	..	75	Recurrence; on last report condition improved
20	40M	3	Entire colon.....	2	45	+	..	100	Had remained free from symptoms at last report
21	30M	2	Entire colon.....	2	42	+	..	75	Carrying on usual occupation at last report
22	29M	0.66	From anus to hepatic flexure.....	3	45	+	..	100	Recurrence; controlled by vaccine; free from symptoms at last report
23	42F	5	From anus to middle of descending colon	2	65	+	..	50	Improved at last report
24	42F	1	Entire colon and terminal ileum.....	2	30	+	..	None	Refused ileostomy; condition unchanged at last report
25	22F	1.5	Entire colon and terminal ileum.....	2	65	+	..	75	Recurrence; taking vaccine at intervals and condition improved at last report
26	54F	2	Entire colon.....	2	56	+	..	50	Colostomy performed because of complicating rectal stricture; improved
27	21F	1	Entire colon.....	2	38	+	..	50	Complicated by adenomatous goiter with hyperthyroidism; improved at last report

of this form of treatment, and with this idea in mind we are reporting the first 50 consecutive cases in which this concentrated serum or antibody solution was employed.

The accompanying table illustrates the salient features of all the cases.

COMMENT

The ages of the fifty patients ranged between 16 and 60 years, but twenty-seven of them were under the age of 30. The duration of the disease varied from six months to eighteen years, but in only nine cases had symptoms been present for less than a year. In thirty-three of the



Fig. 4.—Roentgenograms after the administration of a barium enema obtained in case 5 (tabulation): *A*, the defects and irregularities present on first admission; *B*, the appearance after treatment.

fifty cases, the entire large intestine or the large intestine and the terminal portion of the ileum were involved by the infection. In five, the large intestine from the anus to the hepatic flexure was involved; in two, from the anus to the splenic flexure; in five, from the anus to the middle of the descending colon, and in only five was there no evidence of the disease in roentgenograms made after a barium enema (figs. 3 and 4 and table). The degree of anemia in most of the cases suggests the severity of the disease.

In seventeen cases, there were complications, including multiple polyps, rectal stricture, perirectal abscess, severe intestinal hemorrhage, arthritis, erythema nodosum, endocarditis and duodenal ulcer. It is

impossible to evaluate the effect which these conditions had on the progress of the disease or its treatment without the privilege of personal observation of the patients, but suffice it to say that in some instances they had a profoundly unfavorable effect on the result of the treatment. These are not selected cases, but rather fifty consecutive cases in which the antibody solution was given. However, only four of the twenty-four patients who became free from symptoms had complications, and these complications were of the less severe type. The suggestion is ventured that patients with uncomplicated cases of chronic ulcerative colitis are best treated by attempts to immunize against the causative organism. Results with this form of treatment far surpass other methods, including operation and irrigation of the colon with medicated solutions.

All the patients are living more than a year after treatment with the antibody solution except the one who died following operation for a ruptured appendix several months after becoming free from symptoms of chronic ulcerative colitis.

Twenty-four patients became free from symptoms; thirteen became from 75 per cent to 90 per cent well, and six were improved at least 50 per cent. In only seven cases was there little if any change following the treatment. These seven cases were either severe, long-standing cases with extensive involvement of the colon and destruction, or there were serious complications, such as multiple polyps or strictures.

Certain factors seemed to have a bearing on recurrence of symptoms after patients had become clinically well. One of the significant features seemed to be the failure to remove possible foci of infection. Acute infections of the upper part of the respiratory tract are poorly borne by patients who once have had chronic ulcerative colitis. The extent of involvement, the length of time a patient had had the disease, the age of the patient and his resistance to infection were factors bearing on possible recurrence. Cases of the so-called hemorrhagic type, in which severe hemorrhages occur, respond poorly and are prone to progress poorly. The functional end-result must not be lost sight of. Whereas in some of the cases classified only as "improved" undoubtedly the progress of the infection has been checked, yet strictures and diffuse narrowing of the colon, interfering materially with its powers of proper absorption and elimination, cause difficulty, although the patient's general condition may be excellent. Finally, it is still unfair to speak of "curing" chronic ulcerative colitis; "controlling" is the correct expression. As in many other devastating infections, patients are always obliged to do certain things for their future welfare. Therefore, it seems important that patients who have once overcome an attack of chronic ulcerative colitis should receive the vaccine periodically. Just

28	26F	3	Entire colon.....	2	40	+	..	None	Refused ileostomy; condition unchanged at last report
29	26F	1	Entire colon and terminal ileum.....	2	55	+	—	100	Complicated by perirectal fistula; recurrence; controlled by vaccine; free from symptoms at last report
30	28F	13	Entire colon.....	2	68	+	..	75	Complicated by polyps; marked improvement on last report
31	27M	0.5	From anus to hepatic flexure.....	2	60	+	..	75	Free from symptoms at last report
32	22M	5	Entire colon.....	3	55	+	..	75	Complicated by arthritis; originally 20 bloody stools each day; last report 4 without blood
33	24M	2	Entire colon.....	3	52	+	..	90	Recurrence; ileostomy elsewhere
34	40M	11	Entire colon.....	3	50	+	..	75	Improved at last report
35	36M	0.75	Entire colon.....	2	37	+	—	75	Complicated by exsanguinating hemorrhage; recurrence; ileostomy elsewhere
36	60M	0.75	2	66	+	..	100	Complicated by duodenal ulcer; recurrence; improved by vaccine; free from symptoms at last report
37	31M	10	From anus to splenic flexure.....	2	60	+	..	75	Subsequently markedly improved; relapse with influenza; improved at last report
38	23M	0.75	Entire colon and terminal ileum.....	2	23	+	—	Slight	Complicated by repeated hemorrhages; refused ileostomy; at last report condition little changed
39	32M	1.5	Entire colon and terminal ileum.....	3	60	+	..	50	Ileostomy because of complicating polyposis and extreme rectal stricture; improved at last report
40	24F	2	Entire colon and terminal ileum.....	3	42	+	..	50	Complicated by polyposis and moderate rectal stricture; operation inadvisable; at last report number of stools reduced by one half and bleeding stopped
41	33M	6	Entire colon.....	3	40	+	..	Slight	Complicated by polyposis and rectal stricture; ileostomy before coming to clinic; at last report condition same as at dismissal
42	20M	3	From anus to splenic flexure.....	3	50	+	—	100	Complicated perirectal abscess; free from symptoms at last report
43	23F	1	Entire colon.....	3	43	—	..	None	Complicated by stricture and polyposis; condition unchanged at last report
44	32M	8	From anus to hepatic flexure.....	2	78	+	..	75	Complicated by polyposis; originally from 10 to 12 bloody stools each day; at last report reduced to from 2 to 4 without blood
45	20M	3	Entire colon.....	2	80	+	..	100	Cecostomy before coming to clinic; cecostomy closed surgically after treatment; free from symptoms at last report
46	53M	0.75	From anus to middle of descending colon	2	70	+	..	100	Had remained free from symptoms at last report
47	28F	2	1	48	+	..	75	Free from symptoms at last report
48	49F	8	From anus to middle of descending colon	2	80	+	..	90	At last report from 2 to 3 stools each day instead of usual 1 before illness; otherwise free from symptoms
49	35F	18	Entire colon.....	2	78	+	..	100	Had remained free from symptoms at last report
50	21F	3	Entire colon.....	4	40	+	..	100	Ileostomy before serum used; at last report, 75 per cent improved

THE INFLUENCE OF AURICULAR CONTRACTION ON THE FIRST HEART SOUND AND THE RADIAL PULSE*

CHARLES C. WOLFERTH, M.D.

AND

ALEXANDER MARGOLIES, M.D.

PHILADELPHIA

The present-day clinical evaluation of heart sounds is unsatisfactory. The physical factors concerned in the production of the normal sounds, particularly the first sound, are imperfectly understood. Furthermore, little is known of the mechanisms by which modifications of these sounds are accomplished. It seemed possible, therefore, that studies of patients showing variations of the first heart sound in successive beats might be of interest. This report deals principally with certain of the effects of auricular contraction on the first sound. In this connection it became necessary to consider also the effect of auricular contraction on the amplitude of the pulse wave because of a possible relation between the intensity of the first heart sound and the ventricular output per beat. Wiggers¹ was able to furnish evidence to the effect that when the systolic discharge is increased the first sound is reduced in intensity.

INFLUENCE OF AURICULAR SYSTOLE ON THE FIRST HEART SOUND

It is well known that the intensity of the first heart sound as judged by auscultation may show phasic variation corresponding to the respiratory cycle or may be modified by disturbances in ventricular rhythm such as occur in auricular fibrillation and extrasystolic arrhythmia. In addition to these, however, there are striking variations associated with changes in the time relations of auricular and ventricular systoles.

These variations have received little attention. Griffith² described them in 1911 in two cases of heart block, being particularly impressed by the thumping, emphatic character of some of the beats, the quality of which he compared with that heard in mitral stenosis. In one case he was able to mark the position of the loud beats on a polygram, and he noted that they occurred when the auricles and ventricles contracted

* Submitted for publication, April 22, 1930.

* From the Edward Burton Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania.

1. Wiggers, C. J.: Factors Determining Relative Intensity of Heart Sounds in Different Auscultation Areas, *Arch. Int. Med.* **24**:471 (Nov.) 1919.

2. Griffith, T. W.: Remarks on Two Cases of Heart Block, *Heart* **3**:143 (Feb.) 1912.

how often those periods of treatment should occur is still problematic, but progress in this direction is being made. Recently, with aging of the serum, and improvement in methods of precipitation, we have had more rapid response than in the cases reported in this paper. Enough time has not elapsed for the permanent value of the method to be known.

SUMMARY

The Fasting antibody solution obtained by precipitation in ether-water of the specific immune serum of chronic ulcerative colitis adds a new and valuable reagent to the armamentarium used in the treatment for bacterial chronic ulcerative colitis.

It is particularly efficacious in the treatment of the more severe, subacute cases in which ileostomy was formerly the treatment of choice.

This, in conjunction with the specific vaccine and other symptomatic agents, has greatly reduced the need of ileostomy.

Operation, and primarily ileostomy, has become limited to complications, with very few exceptions.

was constructed for the purpose of studying the time relationships of heart sounds and murmurs. It causes slight distortion as well as magnification of the sounds, as judged by comparison of auscultatory observations directly over the heart and at the output receiver, but we were able to demonstrate, by signalling on tracings, that relative intensities of beats as judged by the stethoscope correspond to variations of the amplitude of the waves recorded (fig. 4). The Wiggers recorder was controlled by phonocardiograms and found to be accurate when care was taken to use sufficiently light reflecting mirrors. Tuning fork vibrations were faithfully recorded up to and including 512 vibrations per second.

Electrocardiograms and sound tracings were recorded on the same strip, parallax being avoided.

CASE 1.—G. L., a white man, aged 49, had been under our observation for one and one-half years. During his first admission to the hospital he had intermittent heart block,⁸ but subsequently the block remained complete. There was a history of acute arthritis (possibly rheumatic fever) at the age of 24 and again at 41. No other etiologic factor for the block was discoverable except possibly

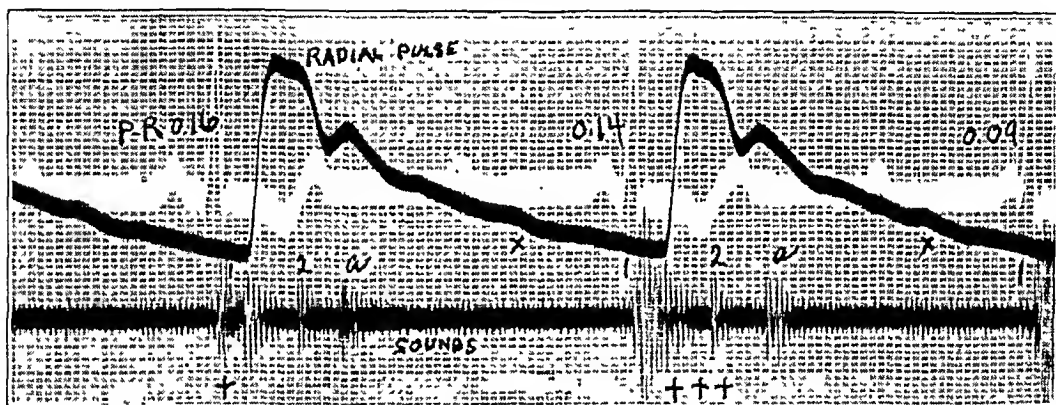


Figure 1—Left

Fig. 1 (case 1).—Complete heart block. Change of intensity of the first heart sound as the P-R interval shortens. The number of plus marks in this and subsequent tracings indicates the arbitrary classification of sounds according to intensity. The first auricular beat during each ventricular diastole is followed by a murmur (a). The sounds are imperfectly recorded because of the presence

some infected roots of teeth which had been extracted before admission. The heart was found by orthodiagram to show moderate generalized enlargement. There was a systolic apical murmur. During the presence of complete heart block, two striking auscultatory observations presented themselves. There was decided variation in the intensity of the first heart sound independent of respiratory excursions, and in addition short murmurs were heard having a rate of from 80 to 90 per minute, which could be timed with a venous wave in the neck. The murmurs were readily shown by tracings to be related to auricular activity (fig. 11).

In figure 1 are shown samples of tracings, indicating the variations in amplitude of the sound vibrations recorded. These changes in ampli-

8. Sudden transitions occurred from normal mechanism to incomplete or complete block. All sequential beats, even during incomplete block, had normal P-R intervals.

at about the same time. He offered the suggestion that for the production of the loud sounds it may be necessary for the auricle to be in systole at the time the ventricle enters into contraction.

Lewis³ stated that when auricular contraction slightly precedes the ventricular, intensification of the first heart sound occurs, but when the relation is reversed reduplication may result. He has published a heart sound record clearly illustrating these points. Lewis pointed out that such variation of the sounds is striking and may be heard in almost any case of dissociation. He regards the variation as a most valuable bedside test of complete heart block when instrumental aids are not available.

A few other observers have noted variations in the intensity of the first sound during heart block. Carter and Howland,⁴ in a report on a child, aged 5 years, with congenital heart block, noted that the first heart sound was usually faint but from time to time a single beat was very loud. The marked accentuation of the sound was interpreted as due to synchronous systole of the auricles and ventricles. Harris⁵ recently reported a case in which complete heart block had existed for at least twenty-eight years. In this patient inequalities of the first heart sound had been noted on the first record and were still present twenty-eight years later. Read⁶ recently reported two cases of complete heart block in which inequalities of the first sound were noted.

We have confirmed Lewis' statement that inequalities of the first heart sound in A-V dissociation are frequently present, and that on auscultation of the heart, are striking enough to be of distinct value in the diagnosis of dissociated auriculoventricular beating. We have also found that the variations may be as striking in ventricular escape as in heart block. It is noteworthy that marked changes in the first sound tend to occur within the normal range of As-Vs time intervals, so that even in normally beating hearts the first sound may be modified according to the length of the interval.

Method.—The apparatus used for the recording of heart sounds consisted of a Western Electric electromagnetic contact transmitter,⁷ a three-stage transformer coupled amplifier with an appropriate frequency-response characteristic, an electromagnetic diaphragm watch case type output receiver⁷ and the Wiggers modification of the Frank segment capsule. This apparatus, which is very sensitive,

3. Lewis, T.: *Lectures on the Heart*, New York, Paul B. Hoeber, Inc., 1915, p. 66.

4. Carter, E. P., and Howland, J.: Occurrence of Congenital Atrioventricular Dissociation: Report of Case of Congenital Heart Block, *Bull. Johns Hopkins Hosp.* **31**:351 (Oct.) 1920.

5. Harris, K. E.: Notes on a Case of Complete Heart Block of Unusually Long Duration, *Heart* **14**:289 (March) 1929.

6. Read, J. M.: Complete Heart Block: Roentgen Kymographic Study, *Arch. Int. Med.* **45**:59 (Jan.) 1930.

7. Dodge, H. F.: *The Stethophone, Electrical Communication*, October, 1924, no. 2, vol. 3; Reprint B-105-I, Bell Telephone Laboratories.

*Comparison of Time Relationships of the Auricular and Ventricular Beats with
the Intensity of the First Heart Sound**

Duration of P-R or R-P Intervals in Seconds		Relative Intensity of Sounds							Height of Recorded Radial Pulse Waves in Millimeters		
		Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	First Strip, Case 1	Second Strip, Case 1	Case 8
R-P	0.28	+
	0.25	+
	0.20	+
	0.15	+
	0.14	+
	0.12	..	+	+
	0.10	+
	0.10	+	+
	0.08	+	++
	0.08	++	+
	0.07	++
	0.06	+
	0.05	..	++
	0.04	+	++	+
	0.03	++	++	++	+
	0.03	..	++	+
	0.02	..	++	++	+
	0.01	+	++	+
	0.00	++	+++	..	+++	+	34.5
	0.00	++	+	35.0
P-R	0.01	+++	+
	0.02	+++	+++	++
	0.02	++
	0.02	++
	0.03	++	+++	35.0
	0.04	+++	+++	+++	+++	+	35.0	21.5
	0.04	+++	..	35.0	22.0
	0.05	++	+	35.0
	0.06	..	+++	..	+++	..	+++	21.5
	0.06	++	21.5
	0.07	+++	+++	21.5
	0.07	..	+++	..	+++	+	35.0	21.5
	0.07	22.0
	0.07	22.5
	0.07	22.5
	0.08	+++	..	+++	+++	++	22.0
	0.08	+++
	0.08	+++
	0.08	++
	0.09	..	+++
	0.10	+++	+++	+++	+++	..	+++	..	36.0	23.5
	0.10	+++	++
	0.11	+++	+++	..	++	++	37.0	24.0
	0.11	+++	37.0
	0.12	+++	+++	..	+++	41.0
	0.12	+++
	0.13	+++	+++	..	+++	++	41.0	25.0
	0.13	+++	25.0
	0.14	++	+++	..	++	++	38.5	26.5
	0.14	+++	..	++	++	39.0
	0.14	++
	0.15	..	+++	..	++
	0.15	++	39.5	41.0	24.5
	0.16	++	..	+++	+++	..	+++	++	39.5	26.5
	0.16	++	++	..	++	++	27.0
	0.16	++
	0.16	+++
	0.16	+++
	0.17	..	++	+++	++	+++
	0.17	++	+++
	0.17	++
	0.18	..	++	+++	++
	0.18	+++	+
	0.18	+++
	0.18	+++
	0.19	++	+	+++	26.5
	0.19	..	+	+++
	0.20	++	..	+++	+	+++	41.5
	0.20	++	+++
	0.20	++	+++
	0.21	39.0	41.0
	0.21	39.5	42.5
	0.21	39.5
	0.22	+	..	++
	0.22	++	+	41.5	28.0

* The data tabulated in each column, except that under case 5, were obtained from a representative continuous strip of tracing. In case 5 the data were obtained from three tracings. The material is arranged according to the lengths of R-P and P-R intervals (first column) measured on the electrocardiograms. The relative intensity of sounds was arbitrarily classified according to the amplitude of the recorded sound waves, + indicating tracings with waves of low amplitude; ++, waves of intermediate amplitude, and +++, waves with the greatest amplitude. The height of the radial pulse waves was measured on the tracings.

tude are not to be regarded as quantitative, but they may be accepted as a rough index of the relative intensity of sounds as judged by auscultation with a stethoscope.

In the accompanying table we have compared the time relationships of the auricular and ventricular beats to the intensity of the first heart sound as indicated by the amplitude of recorded vibrations. The table indicates that first sounds of greatest intensity are recorded when auricular systoles slightly precede ventricular, especially within the P-R range from 0.04 to 0.13 second.⁹ With minor discrepancies, sounds of medium intensity occur on either side of this zone, the limits being a P-R interval of 0.20 second and a R-P interval of 0.03 second. All ventricular systoles failing to have an auricular systole within this range produce faint first sounds.

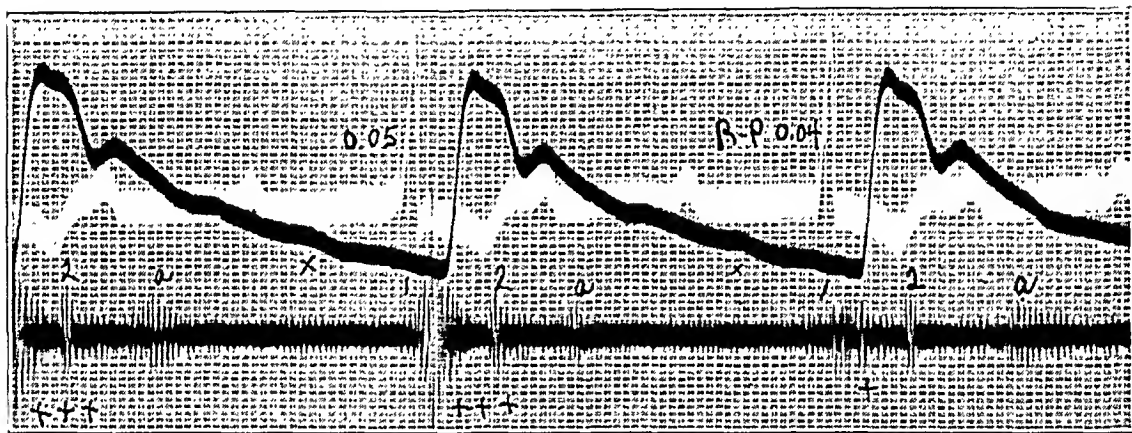


Figure 1—Right

of a constant vibration with a frequency of 175 in the apparatus. That the changes in the first sound are significant is shown by the remarkable constancy of the recorded second sounds as well as the inequalities noted on auscultation. The pulse waves show no significant variations. The points marked *x* show waves due to auricular contraction.

The foregoing relationships are shown graphically in figure 2. The minor discrepancies noted are at least in part attributable to respiratory movement (variable relation of the heart to the wall of the chest) and also to errors in technic, such as variations in pressure on the receiver.

CASE 2.—A. S.,¹⁰ a white woman, aged 53, had intermittent heart block over a period of at least five years, possibly much longer. When the block was complete, marked differences in the intensity of the first heart sound were noted which

9. Our use of the designations P-R and R-P measurements of intervals in this paper does not include the usual connotation of transmission of the impulse. It refers merely to the relative positions of auricular and ventricular systoles as they were measured on electrocardiograms.

10. The clinical data for this patient (case 3) were reported fully by one of us (C. C. W.) and T. M. McMillan (Observations on the Mechanism of Relatively Short Intervals in Ventriculo-Auricular and Auriculoventricular Sequential Beats During High Grade Heart Block, *Am. Heart J.* 4:521, 1929).

were not attributable to respiration. There was a variable systolic murmur, and in addition faint sounds were heard corresponding to auricular beats. Eventually, a very slow idioventricular rate developed, and the patient died. At necropsy, the heart was found within normal limits of size, although there were patchy arteriosclerosis and fibrosis of the myocardium, including particularly the junctional tissues. There was no valvular disease.

In this patient the heart sounds were recorded according to the technic developed by Wiggers, except that a Bowles stethoscope was used as transmitter. No amplification was employed. It is of interest that within the normal range of

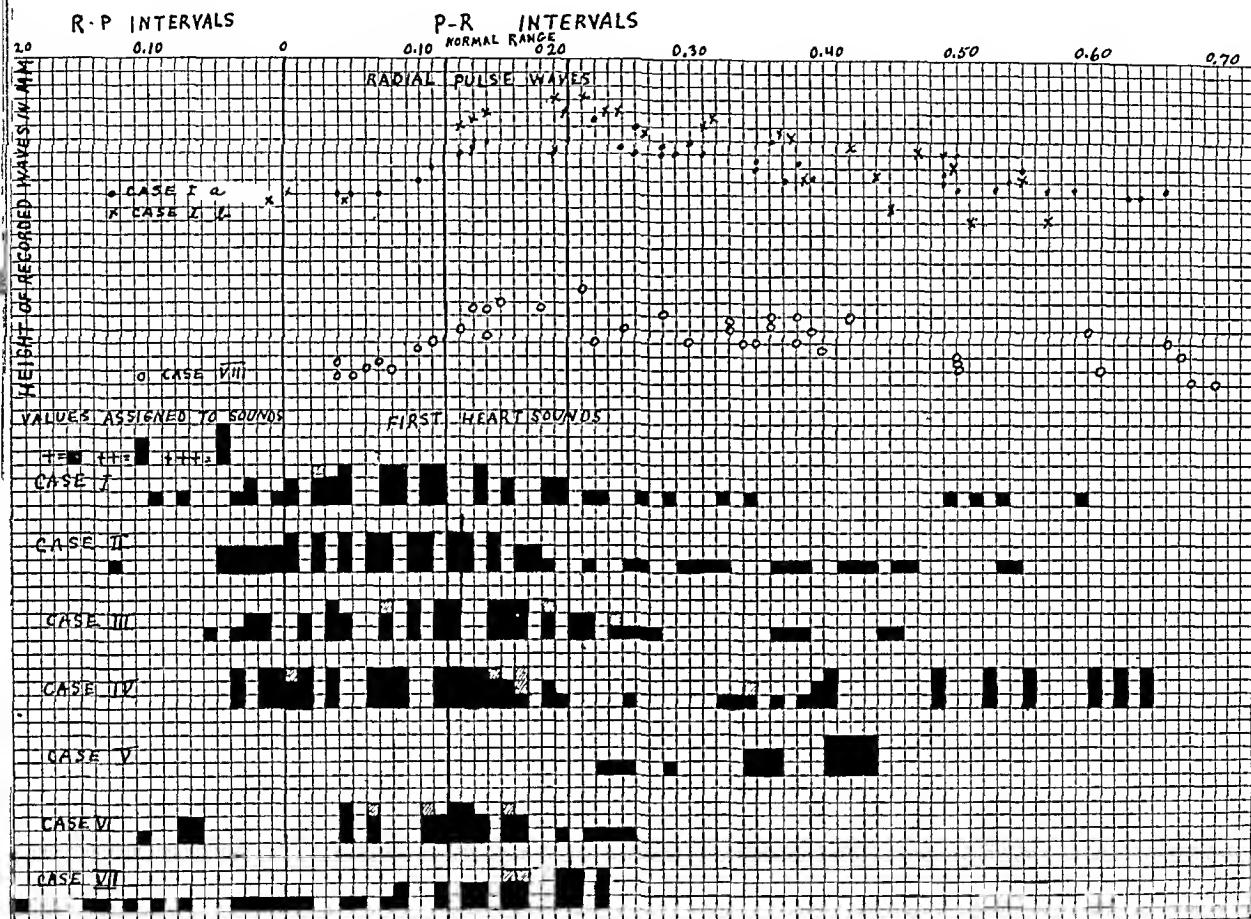


Fig. 2.—The data charted in each instance, except under case 5, were obtained from a representative continuous strip of tracing. The values plotted for the radial pulse waves were obtained by measurements of the height of excursion from the beginning of the upstroke to the peak of the wave. The first heart sounds were arbitrarily divided into three groups according to the relative intensity, as judged from the amplitude of the sound waves. For purposes of charting, a single black square indicates a relatively weak first sound, a vertical column of 3 squares a relatively loud sound, and a column of 2 squares an intermediate sound. Hatching of the column indicates the extent of variability recorded for the P-R interval charted.

P-R intervals the intensity shifted rapidly from loud to faint as the P-R time lengthened. This patient also showed a moderate increase in the sounds when the ventricular beat preceded the auricular by a very short interval. The relationships of varying intensity of sounds to auriculoventricular time intervals are thus similar to those recorded in case 1 (fig. 3 and table).

*Comparison of Time Relationships of the Auricular and Ventricular Beats with
the Intensity of the First Heart Sound *—Continued*

Duration of P-R or R-P Intervals in Seconds	Relative Intensity of Sounds							Height of Recorded Radial Pulse Waves in Millimeters		
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	First Strip, Case 1	Second Strip, Case 1	Case 8
P-R 0.23	..	+	+	+++	24.5
0.24	++	+	+	+	..	40.5	42.0
0.24	+	..	+
0.25	..	+	+	+	+	+	..	38.5	40.0	25.5
0.26	+	+	+	..	+	40.0
0.26	..	+	+	38.5
0.26	..	+	+	38.5
0.27	+
0.27	+
0.28	+	38.0
0.28	38.5	27.0
0.29	..	+	+
0.30	..	+	38.0	40.0	25.0
0.30	39.0
0.31	..	+	38.0	41.0
0.32	+	+	..	+
0.32	+
0.32	+	++
0.33	..	+	..	+	++	26.0
0.33	++	26.5
0.34	+	++	++	25.0
0.34	+	++
0.34	+	++
0.35	37.0	25.0
0.35	37.5
0.36	..	+	+	+	37.5	39.0	27.5
0.36	..	+	39.0	38.5	26.5
0.37	+	+	+	37.0
0.37	36.5
0.38	+	+	+++	37.5	27.0
0.38	+++	25.0
0.39	+	++	+++	36.5	36.5	26.0
0.39	+++	36.5
0.39	+++	36.5
0.40	..	+	..	+++	+++
0.41	..	+	+++	24.5
0.42	..	+	38.5	27.0
0.43	+
0.44	..	+	+	36.5
0.44	+
0.45	..	+	34.5
0.46	+	38.0
0.47
0.48	+	+++	36.0	36.5
0.48	36.5
0.48	38.0
0.49	35.5	33.0
0.49	38.0
0.50	+	37.0	24.0
0.50	23.5
0.50	23.0
0.51
0.52	+++	35.5
0.53	..	+	36.0	36.5
0.53	36.0
0.54	..	+	37.0
0.55	+++	33.0
0.56	+
0.57	35.5
0.58
0.59	+	35.5
0.60	+++	26.0
0.60	+++
0.61
0.62	+	+++	35.0	23.0
0.62	35.0
0.63
0.64	+	+++	35.5
0.65
0.66
0.67	25.0
0.68	24.5
0.68	23.0
0.69	23.0
0.70
0.71
0.72	+++
0.73	+++
0.74
0.75	+++
0.76
0.83	22.0

sounds had maximum intensity (table and fig. 2). The variations of intensity were therefore similar to those of cases 1, 2 and 3 in the short range of P-R intervals, but differed as the P-R intervals increased beyond 0.34 second.

CASE 5.—P. N., an unusually well developed boy, aged 14 years, was seen by Dr. T. Grier Miller during the course of an attack of acute tonsillitis. Dr. Miller reported to us that he was impressed by finding a pulse rate of 60 despite a temperature of from 102 to 103 F. and by the fact that marked differences of intensity in the first heart sound were present, although the rhythm was quite regular. On the basis of these observations we ventured the opinion that the boy had complete heart block. Three days later he was brought to the hospital. At that time the rhythm was irregular, and an electrocardiogram showed incomplete block (fig. 6, top strip). The assumption of a complete block having been present a few days before is therefore not without reason.

The sound tracings showed decided inequalities of the first sound. In the top strip these might be attributed to the ventricular irregularity but strips 2 and 3, which were registered on subsequent days but from the same point on the chest, and which show comparable intensities of the second sound, indicate rather clearly that the sounds are related to the duration of the P-R intervals. In this con-

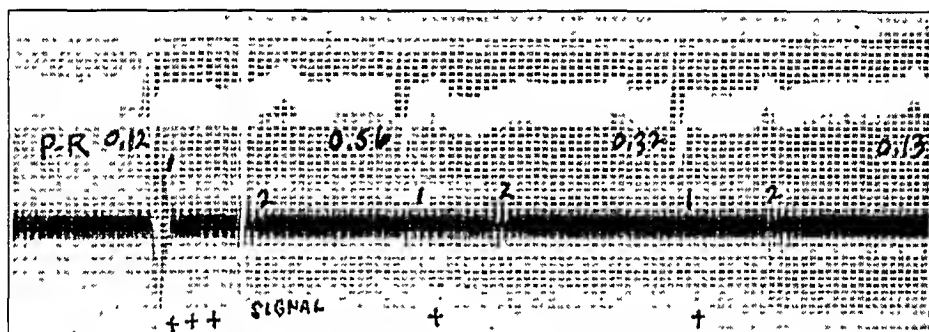


Figure 4—Left

Fig. 4 (case 3).—High grade, almost complete heart block. Variations in first heart sounds corresponding to changes in P-R intervals. The loudest beats,

section it is of interest that although observations of P-R intervals over a wide range were not available, the intensity of the first sound increased as the P-R intervals lengthened from 0.24 to 0.37 second, thus resembling the changes recorded in case 4 but differing from those in cases 1, 2 and 3 (fig. 2).

CASE 6.—C. M., a married woman, aged 32, had been under observation in the cardiovascular section for fourteen months. She complained of faintness on exertion, doubtless due to the fact that exercise produced attacks of paroxysmal ventricular tachycardia. At other times, tracings showed a minor defect in A-V conduction, and ventricular escape was frequently present. When the auricular-ventricular relationships remained constant (sequential beats with P-R intervals of 0.28 second) the sounds were faint, and no marked variations in the intensity of the first sound were discoverable (fig. 7). During ventricular escape, however, marked variations were present which were readily detected by stethoscope and also by examination of the sound records.

The sounds tended to have the greatest intensity when the P-R measurements ranged from 0.04 to 0.13 second (table and fig. 2). When the P-R intervals were from 0.14 to 0.17 second, the sounds were of moderate intensity, and from

CASE 3.—Mrs. S. H., aged 65, had been under observation for five years. She complained of palpitation, dyspnea on exertion, headache and weakness. The heart was moderately enlarged to the left, and there was a systolic murmur at the aortic area. The blood pressure had been consistently high, the systolic readings varying between 190 and 290 mm. of mercury. Four years before examination, high grade heart block developed.¹¹ In July, 1927 (before our attention was attracted to this subject), a note was made on her record that the heart sounds varied in strength.

The variations in the intensity of the first heart sound were the most marked that we have encountered. The faint sounds were heard with difficulty by stethoscope and could scarcely be recorded. The loudest sounds, on the other hand, had an intensity that might properly be classified as normal or average, and the amplitude of the sound vibrations recorded were up to the average that we have obtained by this technic in normal persons (fig. 4).

Sounds of greatest intensity were recorded when the P-R intervals fell in the zone of from 0.08 to 0.20 second. On either side of this zone, there were narrow zones (R-P 0.03 to P-R 0.05 and P-R 0.20 to P-R 0.24) during which sounds of intermediate intensity were recorded. As in almost all of our records, there tended to be some overlapping at the margins (table and fig. 2). When the P-R intervals had a duration of from 0.24 to 0.68 second, the sounds were very faint.

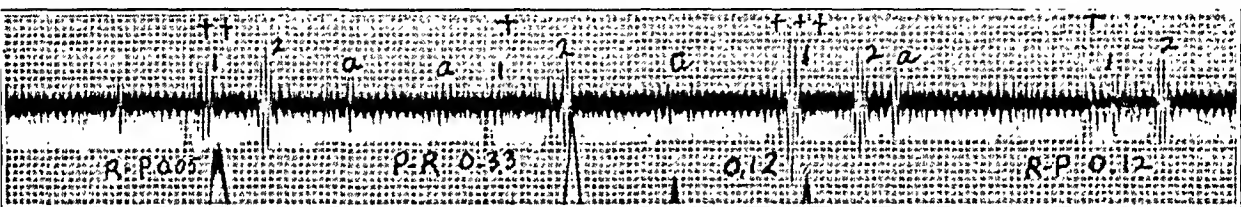


Fig. 3 (case 2).—Complete heart block. Inequalities of the first sound associated with changes of P-R intervals. They were recorded without amplification, according to the technic described by Wiggers, except that a Bowles stethoscope was used as a transmitter.

CASE 4.—F. D., aged 6 years, was a fairly well grown, healthy-looking girl. A marked bradycardia had recently been discovered by accident. Its duration was not known, since it had caused no symptoms, and no previous examination of the heart had been made. An electrocardiogram showed complete heart block with an auricular rate of 82 and a ventricular rate of 46. By orthodiagram the heart revealed a slight generalized enlargement. There was a systolic murmur at the apex. No diastolic murmur could be heard. Decided variations in the intensity of the first sound were noted.

Comparison of the electrocardiogram and sound tracing (fig. 5) revealed the following: The sounds were comparatively faint when the P-R measurements had a range of from approximately 0.18 to 0.34 second. On either side of this zone (P-R intervals of from 0.14 to 0.18 second and from 0.34 to 0.39 second) the sounds tended to have moderate intensity although some variations were noted. In all other relationships of auricular and ventricular beats recorded, the first

11. The heart block has never been quite complete. Auricular beats falling within a certain time zone following ventricular beats were transmitted, causing some ventricular irregularity. The mechanism bears some resemblance to what has been described as the supernormal phase of conduction, and this feature of the case will be reported later.

waves might be found to correspond with the variations in the intensity of the first sound. Read⁶ recently found differences in the shape of the waves of left ventricular excursion (roentgenograms) during complete heart block, which he attributed to variations in the number of auricular systoles during ventricular diastole. In addition, he surmised that inequalities of the first heart sound at successive systoles suggest a variability of stroke volume. This point will be referred to later. As far as we are aware, however, there is no actual evidence to be found in the literature suggesting a correlation between the intensity of the first heart sound and the amplitude of the pulse wave, except that reported by Wiggers.¹

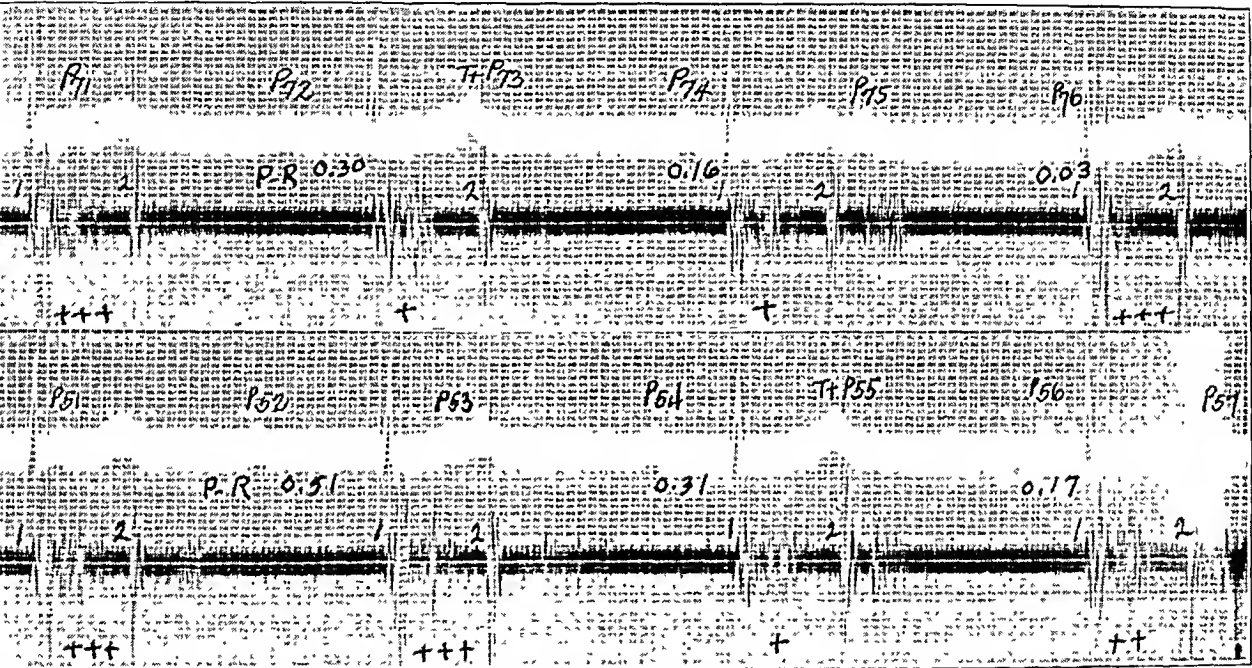


Fig. 5 (case 4).—Complete heart block. Variations in the first heart sounds and their relations to the length of the P-R intervals.

The experiments of Gesell¹² indicate the possibility that there might be a relationship between the duration of P-R intervals and the amplitude of pulse waves. It has been found by several investigators that auricular systole is capable of increasing ventricular output over that maintained by venous pressure alone, but Gesell discovered in addition that auricular systole varied in effectiveness in increasing ventricular output, depending on the time relation of auricular systole to ventricular

12. Gesell, R. A.: Auricular Systole and Its Relation to Ventricular Output, *Am. J. Physiol.* **29**:32 (Nov.) 1911; *Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation and Stimulation of the Vagus Nerve*, *ibid.* **40**:267 (April) 1916.

0.20 to 0.25 they were comparatively faint. It is also of interest that three beats with R-P intervals of 0.08, 0.08 and 0.17 second caused sounds of moderate intensity but one with a R-P interval of 0.11 was faint. Thus in the range of auriculo-ventricular relationships during which observations could be made the variations of sound intensity were similar to those of cases 1 to 4, inclusive.

CASE 7.—L. G., an unmarried woman, aged 29, was referred for study by the thyroid section to the cardiovascular section. A subtotal thyroidectomy had been performed two years previously. This operation had apparently completely relieved the hyperthyroidism from which she had been suffering; nevertheless, she had not completely regained her strength. Our observations included a decidedly enlarged heart, aortic regurgitation and mitral stenosis. The valvular disease was probably of rheumatic origin, although there was no history of rheumatic fever. The blood pressure was 130 systolic and 60 diastolic. There were no congestive phenomena but the margin of cardiac reserve was narrow.

It was possible to make only one examination of this patient. Our attention was attracted by a slight arrhythmia and on auscultation by marked variations in the intensity of the first heart sounds. These variations are shown in figure 8, figure 2 and the table. Vibrations of greatest amplitude were recorded when the

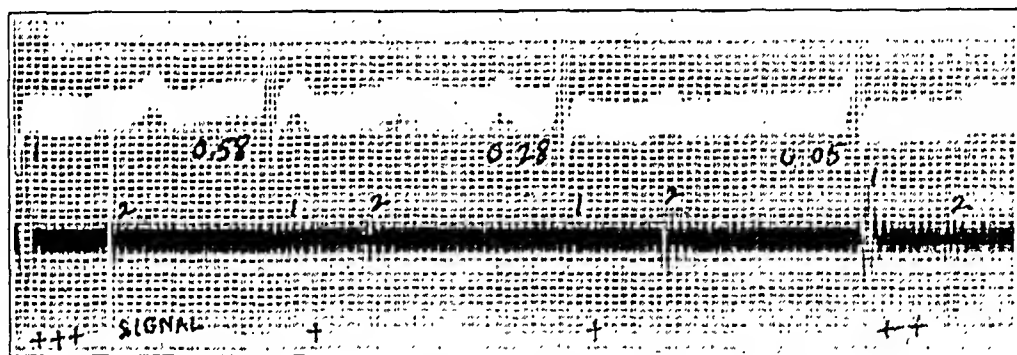


Figure 4—Right

as judged by auscultation, were signalled on the tracing (vertical broad white lines).

P-R measurements were from 0.16 to 0.23 second. In the zone of P-R measurements ranging from 0.08 to 0.16 second the sounds were of moderate intensity, while from 0 to 0.07 the sounds were relatively faint. All beats the ventricular systole of which preceded auricular systole had relatively faint first sounds.

In this patient the relationships of change in sound intensity to auriculoventricular intervals were different from those observed in other cases. Instead of diminishing intensity as the P-R interval increased in the normal range, the sounds tended to become louder. In this connection it should be pointed out that this is the only patient in the series in whom mitral stenosis was detected.

INFLUENCE ON AMPLITUDE OF THE RADIAL PULSE WAVE

In view of the marked differences in the first heart sound recorded in case 1, it seemed worth while to make records of the radial pulse wave in order to discover whether any differences in amplitude of pulse

In this connection it is of interest to note that Griffith² described pulsus alternans in a patient with high grade heart block and slow ventricular rate. There was from 3 to 2 block with the auricular systoles so placed that every second ventricular beat quickly followed auricular contraction. This relationship was associated with the larger pulse waves. The alternate ventricular systoles were not immediately preceded by auricular beats, but the two occurred practically simultaneously. Under these circumstances, smaller pulse waves might be due to the time relations of auricular and ventricular systoles.

Method.—An ordinary pulse-recording tambour from the Jaquet polygraph was strapped about the wrist with the button placed over the radial artery. The

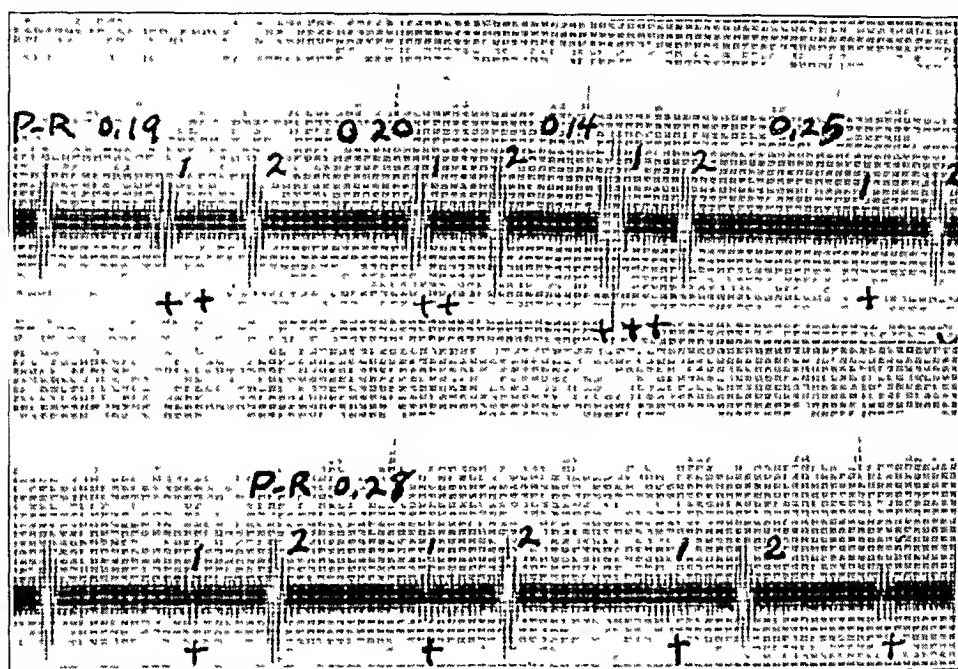


Fig. 7 (case 6).—Ventricular escape. Marked variations of intensity of the first sound are present, depending on the duration of the P-R interval. When the rhythm is regular and the P-R intervals are prolonged (lower strip), the sounds are uniformly faint.

tambour was connected by a rubber tube with the Wiggers modification of the Frank segment capsule. Simultaneous electrocardiograms and pulse curves were made, and in some tracings sound records were included. In the tracing that includes electrocardiograms, pulse waves and sound vibrations, the arrangement of mirrors was such that slight parallax was present. This has no bearing on our observations.

In case 1 the pulse wave tracings showed marked differences in their duration (from the beginning of the upstroke to the dicrotic notch) and shape (fig. 9). The waves of greatest amplitude tended to be the longest. The variations in the pulse waves were found to bear

systole. He found that auricular systoles completed from 0.008 to 0.02 second before ventricular systole is begun seem to have the greatest effect, although even those auricular systoles partly "stoppered" by ventricular systole have a positive effect on the filling of the ventricles. Auricular systoles occurring entirely within ventricular systole have no effect, while those occurring in ventricular diastole increase in effectiveness from nothing to maximum as they approach the beginning of ventricular systole.

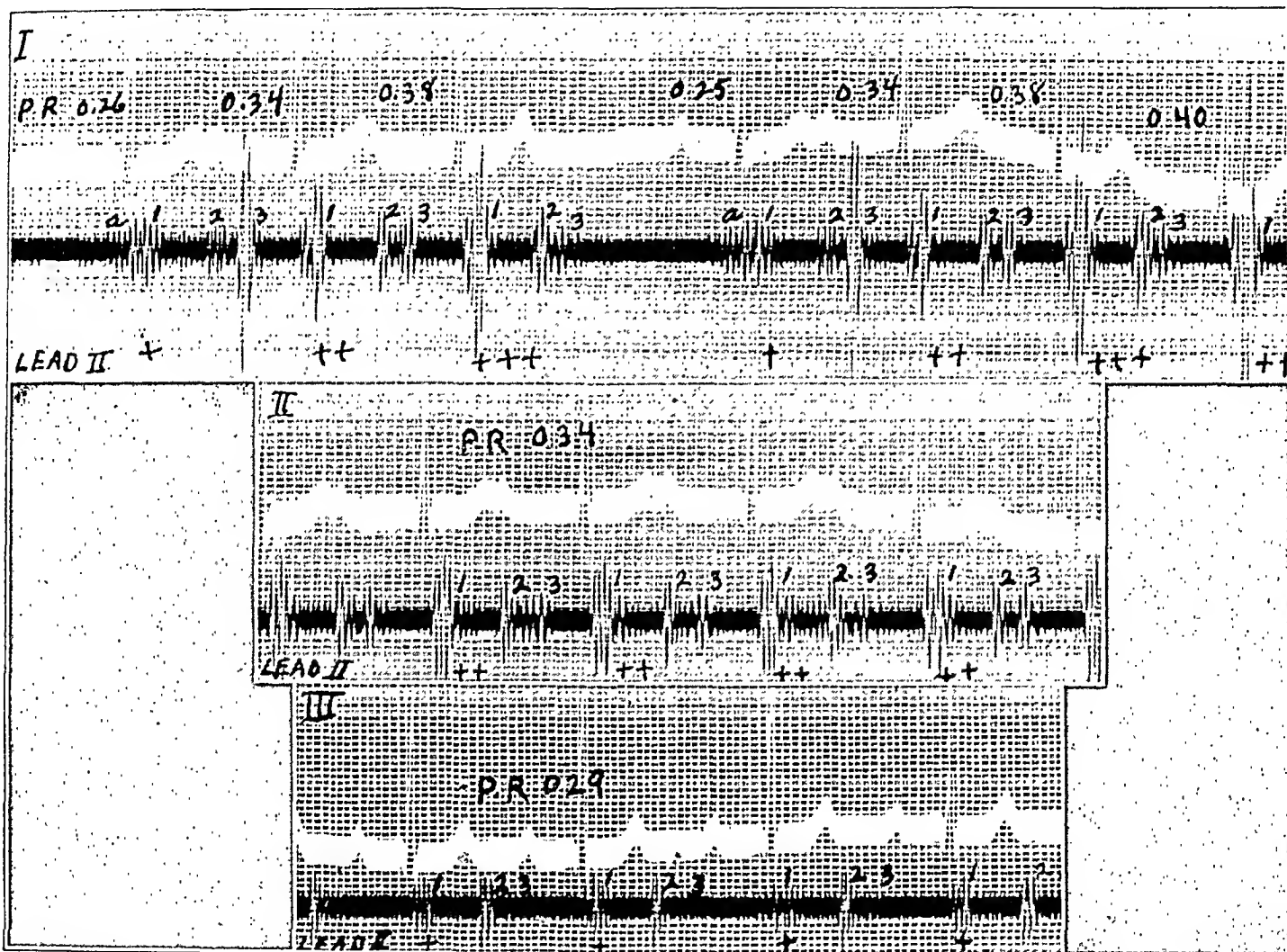


Fig. 6 (case 5).—The top strip shows incomplete heart block. The lower strips, which were made on subsequent days, show prolongation of P-R intervals but no dropped beats. Marked variations in the first sound are recorded in the top strip. In strip II, in which the P-R intervals have a duration of 0.34 second, the first sound is comparable with those beats in strip I having a P-R interval of approximately 0.34 second. In strip III with P-R intervals of 0.29 second the first sound is comparable with the beats in strip I having a P-R interval of from 0.25 to 0.26 second. There are also extraordinary changes in the third heart sound depending on the relation of the auricular contraction to the end of the ventricular systole.

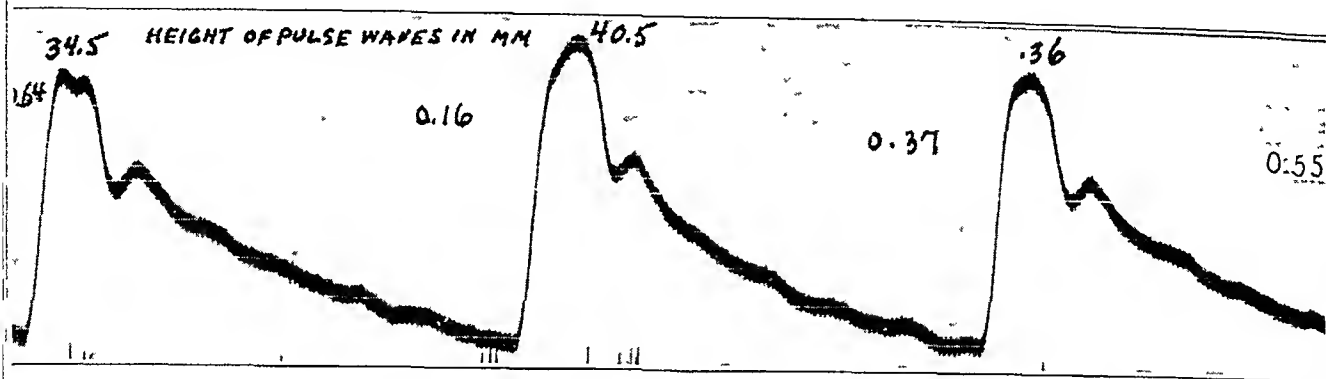


Fig. 9 (case 1).—The relation between the size of the

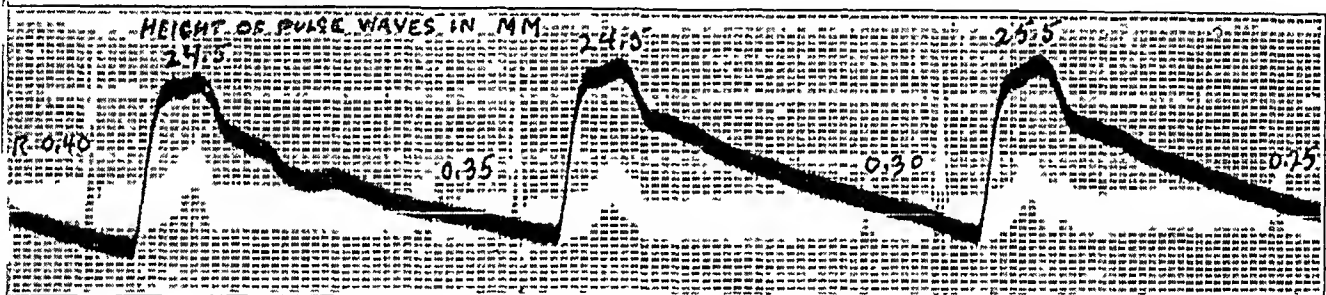


Fig. 10 (case 8).—The relation between the size of the

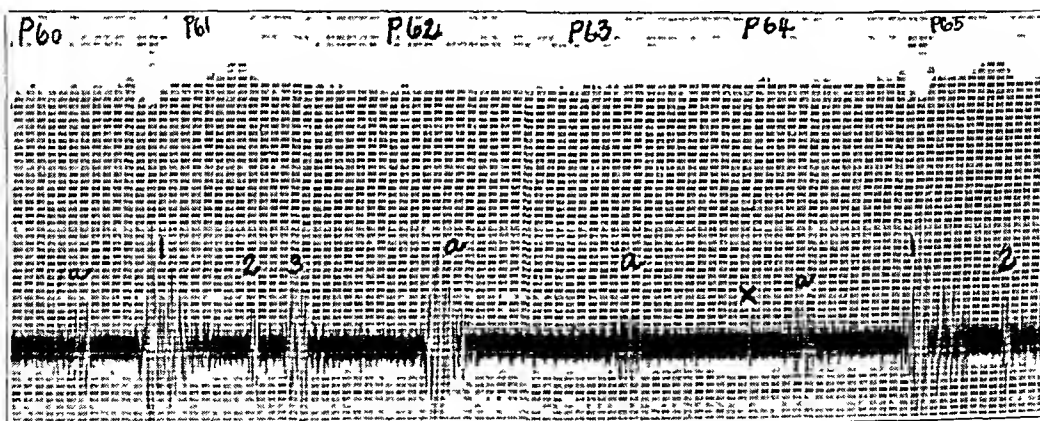


Fig. 11 (case 1).—The tracing shows a murmur following each P wave. those in late diastole. When this murmur coincides with the third heart sound,

a definite relationship to the duration of the intervals between ventricular systole and the preceding auricular systole (table and fig. 2). When these intervals were very short (less than 0.1 second), smaller pulse waves were recorded. Between 0.10 and 0.13 second, increase in size of pulse waves occurred. The optimum P-R range was approximately from 0.12 to 0.31 second, after which a gradual decline in amplitude of pulse occurred.

Numerous pulse tracings were made of this patient, and all but two showed the type of variation described with similar relations to the P-R intervals. The comparative magnitude of the variations differed from day to day. In the two exceptional tracings no significant variations in amplitude were discoverable (see pulse tracing, fig. 1).

Pulse tracings were also made in cases 3, 4 and 6. In case 4, no significant variations in amplitude were recorded. The pulse waves in cases 3 and 6 were more difficult to analyze because of ventricular

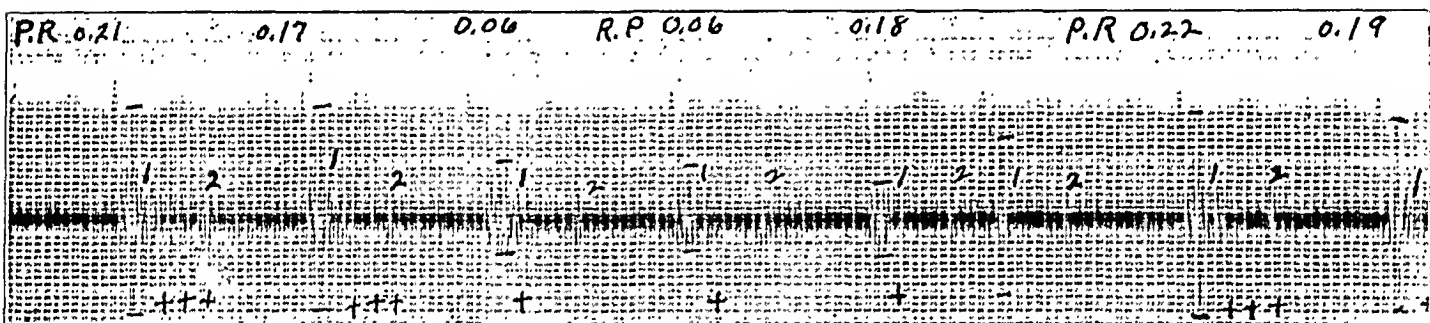


Fig. 8 (case 7).—Ventricular escape. Marked variations of intensity of first sound depending on the duration of the P-R intervals. The usual relations are reversed, possibly due to the presence of mitral stenosis.

irregularity. After a careful study of these tracings, we were unable to make out any significant relation to the duration of P-R intervals.

CASE 8.—R. W., a married woman, aged 35, had had complete heart block for nine years. The etiology of this condition was uncertain. The heart was only slightly enlarged, and there was a fairly distinct systolic apical murmur. By auscultation decided differences in the intensity of the first heart sound were easily detected, but unfortunately, owing to temporary trouble with the apparatus, satisfactory sound tracings were not obtained.

A sample of radial pulse tracing is shown in figure 10. The amplitude of the waves in relation to the length of P-R intervals is given in the accompanying table and is shown graphically in figure 2. Minor variations in amplitude independent of the duration of P-R intervals were also recorded. Nevertheless, the table and figure 2 show a distinct influence of P-R intervals on the amplitude of the waves. When the P-R intervals were below 0.10 second, the pulse waves had the smallest amplitude. The amplitude increased as the P-R interval lengthened. The largest pulse waves were recorded in a range of approximately from 0.14 to 0.42 second. Beyond 0.42 second a decline in the height of the pulse waves appeared to begin, although unfortunately the observations are too few in

this area to permit detailed analysis. The trend in the amplitude of the pulse waves continued downward as the P-R interval lengthened. It was of interest that higher pulse waves were recorded when the P-R interval was as long as 0.6 second than when it was under 0.1 second.

The curve of pulse amplitude in its relation to the duration of the P-R interval is in general similar to those obtained in case 1. The time relationships of the increase in amplitude of pulses are practically identical in the two cases, but the downward slope is more gradual in case 8.

COMMENT

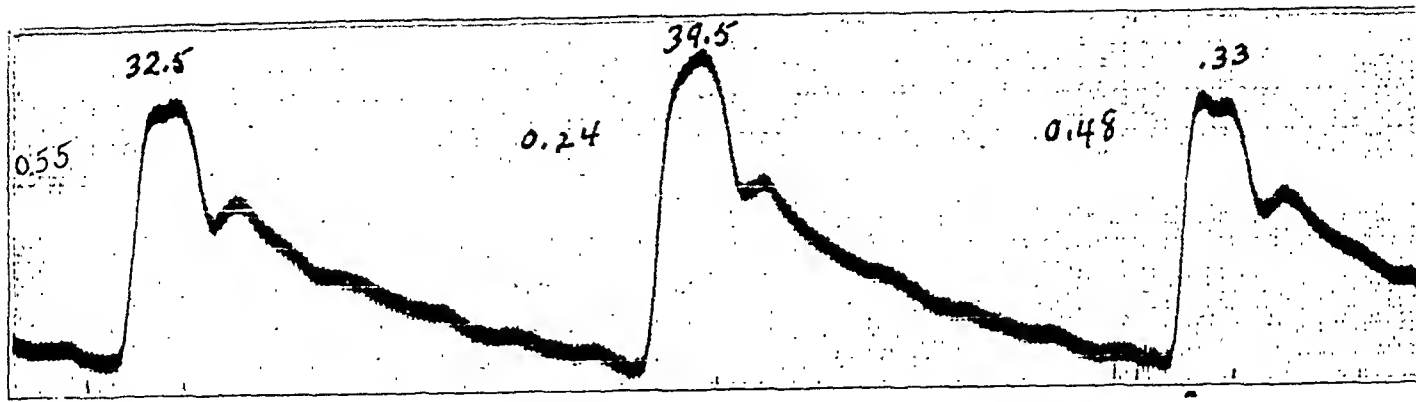
Variations in Pulse Waves.—After having recorded in case 1 definite variations in the amplitude of pulse waves, and observed the relation of these variations to the duration of P-R intervals, we anticipated that similar observations might be frequent in cases with dissociated beating of the auricles and ventricles. We observed them, however, in only one of four other cases. Furthermore, even in case 1, in which the opportunity was afforded for making many tracings, at least two curves showed no significant differences in the amplitude of the pulse waves. It is possible that had we been able to repeat the studies more often in the other patients, we might have recorded variations.

The lack of consistency in the range of pulse wave variations from day to day, despite the insignificant changes in either auricular or ventricular rates, suggested that some factor that we failed to recognize was operative. Possibly, this factor may have been the height of venous pressure, by which, according to Henderson and Barringer,¹³ it is determined whether or not auricular systole has any appreciable influence on ventricular filling.

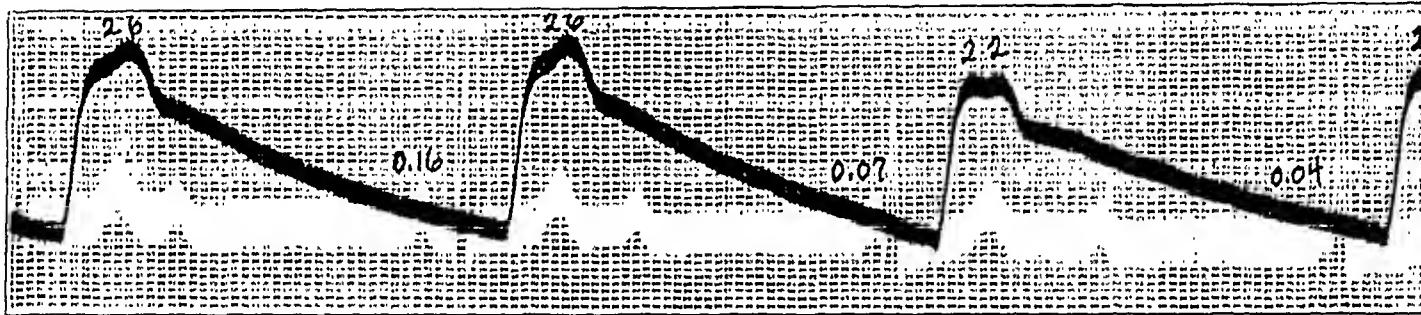
The work of Gesell¹² probably furnishes the best clue to the variations in amplitude of pulse waves. He brought forward evidence for the view that increased ventricular output resulting from auricular systole is the result of such factors as increased initial tension of the ventricles, lengthening of the fibers and altered surface volume relation.

Our studies could not be expected to yield any direct evidence bearing on this point; nevertheless, an accidental observation in case 1 seems to deserve mention. It was stated in the protocol of case 1 that short murmurs were heard corresponding to the auricular beats (fig. 11). The distinctness of these murmurs varied according to their position in ventricular diastole; those occurring early were easily heard and recorded while those occurring in the latter part were less distinct and frequently could not be recorded. The murmurs that were readily recorded began from 0.14 to 0.16 second after the beginning of the P-wave and persisted approximately from 0.10 to 0.16 second. We may

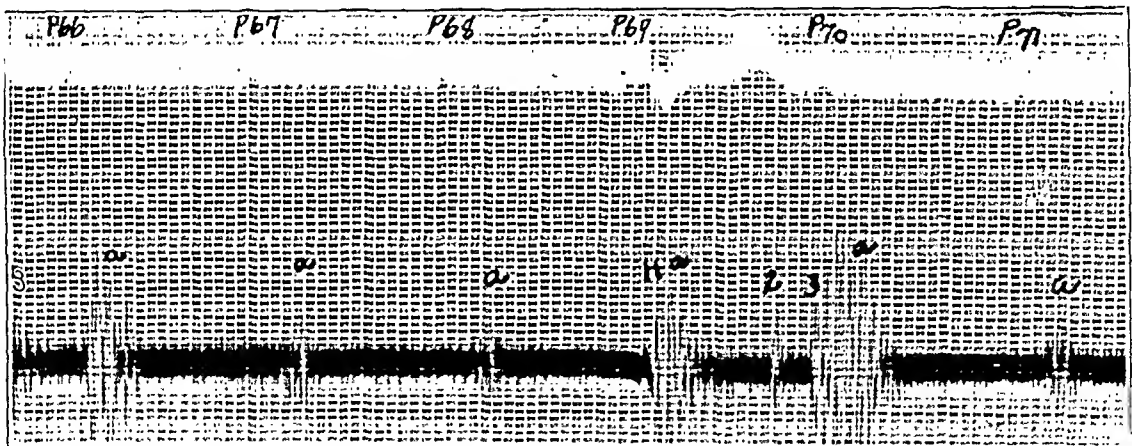
13. Henderson, T., and Barringer, T. B., Jr.: The Relation of Venous Pressure to Cardiac Efficiency, *Am. J. Physiol.* **31**:352 (March) 1913.



pulse waves recorded and the duration of the P-R intervals.



pulse waves recorded and the duration of the P-R intervals.



Those falling in early ventricular diastole are louder and more prolonged than a very loud and prolonged murmur occurs.

But R intervals were recorded) there was remarkable similarity in the reduction of sound intensity toward the long side of the normal P-R range. The decline to faint sounds was in some cases completed within the normal P-R range, but in others was delayed until the P-R interval was as long as 0.24 second.

In these five cases the sounds were of maximum intensity when the P-R intervals were very short. In cases 1, 2, 3 and 6, it was possible to study the time relationships of the increase in sounds. In all of these cases moderately increased intensity occurred even when ventricular electric systole preceded the auricular systole by a few hundredths of a second. When auricular systole slightly preceded ventricular, and in one case in which the two were simultaneous, maximum sounds occurred. These relationships are shown in figure 2.

With markedly prolonged P-R intervals two distinct types of sound variation were noted. In the two young patients (cases 4 and 5), when the P-R interval reached 0.34 and 0.32 second, respectively, the sounds began to become louder. Of the three older patients in whom observations could be made during this range, none showed the late increase of sound intensity.

The differences in relationship of the changes of sound intensity to the duration of the P-R intervals in the patient with valvular disease (case 7, mitral stenosis and aortic regurgitation) were striking. Instead of loud first sounds in association with very short P-R intervals, as the other cases showed, they were relatively faint. As the P-R intervals lengthened toward the upper range of normal, the sounds increased. Thus the relationship seemed to be just the reverse of those recorded in the nonvalvular cases.

Factors Concerned in Variations of the First Sound.—Griffith's² suggestion that for the production of the loud sounds it may be necessary for the auricle to be in systole at the time the ventricle enters into contraction is shown by figure 2 to be inadequate. Nevertheless, he deserves full credit for making this observation with the methods of study available. We have thus far not observed the reduplication of the first sound mentioned by Lewis³ when ventricular slightly precedes auricular contraction, although we have recorded it when the reverse relation is present.

We have discussed our reasons for accepting the view that the differences in amplitude of pulse waves recorded are due largely to such dynamic factors as the degree of ventricular filling and initial tension. It is obvious from the time relationships of the changes of intensity of sounds that such factors must assume at most a minor rôle in causing the inequalities of sound. Consequently, Read's⁶ recent suggestion that the inequalities of sound are associated with varying ventricular outputs receives no support from our work.

assume that these murmurs represent vibrations produced by the blood flow from the auricles to the ventricles following an auricular beat.¹⁴ Their time incidence is in a zone approximately from 0.14 to 0.30 second after the beginning of the P wave. This zone corresponds to the period during which the largest pulse waves are present. Physiologic evidence supports the view that both initial intraventricular tension and ventricular content (which determines the length of the fibers and the altered surface volume relation) are factors of importance in the efficiency of the heart beat. If only ventricular content were concerned, pulse waves would be expected to continue to increase in size as ventricular systole fell later in the period of active flow from the auricles to the ventricles; this, however, was not the case, as the pulse waves tended to be as large when ventricular systole coincided with the early part of the period of inflow resulting from auricular systole. At such a time one might expect greater change in ventricular initial tension than filling.¹⁵ The gradual decline in amplitude of pulse waves as ventricular beats fell later and later in the period of auricular diastole, however, could scarcely be attributed to changes in initial tension. This decline is probably related mainly to differences in degree of ventricular filling.¹⁶

It will be noted that while the size of the pulse waves bears a definite relationship to the P-R measurement, other minor variations are present. For these lesser variations there are at least three possible causes: (1) defects in technic of recording (movements of wrist, etc.), (2) respiratory variations and (3) completeness of ventricular emptying in the preceding beat.¹⁷

Variations in Sound Intensity.—With the exception of relatively minor discrepancies, the variations of intensity of the first sound in all seven cases studied bore an unmistakable relation to the length of the P-R intervals. In five of the seven cases (all except those of the woman with mitral and aortic valvular defects and the boy in whom no short

14. This view is based on the time incidence of the murmurs in this and other cases and the fact that they are loudest in early ventricular diastole when the greatest blood flow from auricles to ventricles is possible.

15. Wiggers, C. J.: *The Pressure Pulses in the Cardiovascular System*, New York, Longmans Green & Company, 1928, p. 55.

16. Wiggers (The Circulation in Health and Disease, Philadelphia, Lea & Febiger, 1923, p. 96) stated that if the As-Vs interval is sufficiently long, volume curves show a back flow from ventricles to auricles. Ventricular filling might therefore be expected to reach a peak at the end of the period of blood flow caused by auricular systole and then temporarily decline.

17. There was slight auricular arrhythmia in case 1 so that constant or predictable A-V relationships were not maintained. Thus the beats having a certain time relation might be preceded by beats with varying intervals and consequently varying emptying.

of sound, which occur within the normal range of P-R intervals and slightly beyond it, could be definitely related to movements of the mitral leaflets from a position near the closure to the opening. It will be noted that in each instance the transition period (sounds of intermediate intensity) is extremely brief.

On the basis of what knowledge we have regarding the dynamic factors concerned in contraction, we are unable to account for the fact that in three of our cases (cases 1, 2 and 3) the first sounds remain relatively weak when the P-R intervals are long, whereas in two cases (cases 4 and 5) they assume the maximum intensity. It occurred to us that possibly the variable factors in these two groups of cases might also be the position of the mitral leaflets.

The two patients who had maximum sound intensity with long P-R intervals were both children with presumably thin, pliable leaflets which might more readily float back toward a position of closure during the period of relative inactivity than the leaflets of the older patients. We have no evidence for this assumption, but no other reasonable explanation for these variations in sound presents itself.

A moderate increase of sound intensity occurred regularly in four cases (cases 1, 2, 3 and 6) when ventricular electric systole preceded auricular systole by a few hundredths of a second. Obviously, these changes in sound must be the result of auricular contraction, but it does not seem reasonable to suppose that either change in position of leaflets or any change in the ventricular status could have been brought about by auricular systoles with this time relationship. It seemed to us, therefore, that there might be significance in the fact that as ventricular pressure was rising as a result of contraction, auricular pressure was also beginning to rise. These conditions could be expected to minimize regurgitation of pressure from the ventricles and thus favor a more rapid rise of intraventricular tension (and therefore a louder sound).

It is fairly generally accepted, although not clearly established, that closure of the A-V valves furnishes a component of the normal first heart sound. It is necessary, therefore, to consider what part valve closure might play in the variations that have been described. No direct evidence can be furnished on this point. It would seem certain, however, that valve closures cannot contribute to the increase of the first sound, which was repeatedly observed when ventricular systole slightly preceded auricular. Furthermore, if variations in the valvular element of the first sound were important one would expect the loudest sounds when the beginning of ventricular systole found the leaflets widely open (permitting momentum to be acquired during closure) and the faintest sounds when the leaflets were already near a position of closure. If the results of Dean's²⁰ experiments on the time incidence of valve movements may be applied to the human heart, the ventricular

It may be assumed as a provisional hypothesis that the inequalities of sound depend on the position of the mitral leaflets at the beginning of ventricular contraction. The data available do not warrant an attempt to elaborate this hypothesis, but there are certain facts in support of it deserving mention.

Wiggers¹⁸ stated that the sound intensity varies directly as the systolic tension developed within the ventricles, and there is good reason to believe that it is with the tension developed during the isometric period of systole.

This statement at once suggests the possible importance of the position of the mitral leaflets at the beginning of ventricular systole in modifying the first sound. If the leaflets happened to be widely open, at least slight regurgitation might occur, thus retarding the development of intraventricular tension.¹⁹ If, however, the leaflets happened to be near a position of closure at the beginning of ventricular systole, little or no regurgitation might be expected to take place, thus permitting a more rapid rise of intraventricular tension and consequently a louder first sound.

It is a well known clinical fact that the presence of mitral insufficiency tends to weaken the first sound and frequently obliterates it entirely. On the other hand, mitral stenosis with its relatively rigid mitral leaflets is usually accompanied by a sharp loud first sound. If, however, regurgitation is associated with stenosis the sharpness of the first sound tends to be lessened and with marked regurgitation may be completely obliterated.

There is direct evidence to the effect that the position of the mitral leaflets is altered by auricular systole. Dean's²⁰ curves of movements of the leaflets appear to show that shortly after the beginning of auricular systole they tend toward a position of closure (up to 0.147 second) but quickly open. These experiments were done on perfused cats' hearts; consequently, one might venture the assumption that in human beings with larger hearts and consequently larger leaflets, the period in some cases might be prolonged a few hundredths of a second. If such an assumption is justified, the curves of decreasing intensity

18. Wiggers, C. J.: *The Circulation in Health and Disease*, Philadelphia, Lea & Febiger, 1923, p. 324.

19. One would expect very little regurgitation of blood, but there might be no inconsiderable regurgitation of pressure. The experiments of C. J. Wiggers and H. S. Feil (*The Cardiodynamics of Mitral Insufficiency*, *Heart* 9:149 [April] 1922) show surprisingly little alteration in the dynamics of ventricular contraction in the presence of mitral regurgitation. It seems possible, however, that slight changes in the development of intraventricular tension might have an important influence on the first heart sound.

20. Dean, A. L., Jr.: *Movements of the Mitral Cusps in the Cardiac Cycle*, *Am. J. Physiol.* 40:206 (April) 1916.

contraction. The penetrating researches of Wiggers¹⁸ in this field have lent some support to this view. It is generally appreciated that such factors as the thickness of the wall of the chest and the presence or absence of valvular defects must be discounted before significance is attached to the intensity or the quality of the sound.

We wish to offer the suggestion that the duration of the auriculo-ventricular interval within the normal range may have importance in determining the character of the sound. This suggestion is strongly supported by the evidence we have obtained in our cases of dissociated beating. Thus it is probable that the loud first sounds so frequently heard when the P-R intervals are short (approximately from 0.12 to 0.15 second) owe part of their intensity, at least in some cases, to the proximity of the auricular and ventricular contraction. It is equally probable that in certain cases with longer P-R intervals (approximately from 0.18 to 0.21 second) the relatively weak first sound is affected by the length of the period between auricular and ventricular contractions.²³

We do not wish to stress unduly the importance of the auriculo-ventricular interval in determining the character of the first heart sound. It is only one of a number of factors involved, and under certain circumstances not well understood may vary or be entirely negligible (as was shown in case 1). Nevertheless, it is a factor that should be reckoned with, and failure to do so may vitiate clinical deductions based on the character of the first sound.

SUMMARY

1. A series of seven cases with varying auriculoventricular relationships all showed inequalities of the first heart sound which could be related to the lengths of the intervals between auricular and ventricular systoles. These time relations tended to be characteristic for each case, although the degree of inequality varied and exceptionally could not be recorded.

2. The inequalities of sound are easily detected by auscultation and furnish a valuable clinical test of dissociated beating of the auricles and ventricles (complete heart block and ventricular escape). The absence of inequality of sound does not rule out the possibility of dissociated beating.

3. In two cases (both having complete heart block) inequalities in the size of the pulse waves were recorded. When the amplitude of the waves recorded was compared with the lengths of intervals between auricular and ventricular systoles, a definite relation was revealed. In

23. The evidence obtained in a study of the inequalities of the first sound of extrasystoles (to be reported) also points to the importance of As-Vs relations as a factor governing the intensity of the sound.

beats associated with loud sounds and short P-R intervals would begin with the leaflets near the position of closure. Faint sounds occurred in case 1 when the evidence indicated that the blood was flowing rapidly from the auricles to the ventricles, so that the leaflets could not have been near closure.

The changes in intensity of sound in our patient with mitral stenosis and aortic regurgitation were of particular interest in that the time relationships of change were so different from those of all other cases. A sound tracing recently published by Schellong²¹ made from a patient with mitral stenosis and incomplete heart block showed inequalities of the first sound. The P-R intervals of the accompanying electrocardiogram were all longer than those observed in our patient with mitral stenosis, so that the two cannot be compared directly, although the data in the two cases are in a sense complementary. The curves can be compared with those of our case 5 in which there was no evidence of mitral stenosis, but incomplete block with the P-R intervals of similar duration was present. In Schellong's case the intensity of the first sound was greatest when the P-R interval was only slightly prolonged (0.23 second), but with longer intervals the intensity was reduced. This is just the opposite relation to that observed in our case 5, thus suggesting that mitral stenosis was responsible for the difference. If the observations in Schellong's case are added to those of our subject with mitral stenosis (case 7, fig. 2) a curve is obtained suggesting that mitral stenosis causes a delay in the curve of rise and fall of intensity of the first sound with reference to the duration of the P-R intervals. Further observations on patients with mitral stenosis and shifting As-Vs relations will be necessary to establish this point.

Clinical Significance of Inequalities of the First Sound.—We have mentioned that the inequalities of sound may be utilized as an auscultatory sign of dissociated beating (heart block or ventricular escape.²²). Their recognition on auscultation depends solely on whether one remembers to compare the intensity from beat to beat. When the clinical test is made, it is advisable to have the patient hold his breath for periods long enough to exclude variations due to respiration.

The fact that marked inequalities of sound may occur within the normal range of auriculoventricular relations (fig. 2) would appear to have wide clinical significance. There is a tendency among clinicians, perhaps not without justification, to attach importance to the characteristics of the first sound as evidence of the vigor of ventricular

21. Schellong, F.: Mitral Stenosis Murmur in Conduction Disturbance, *Klin. Wchnschr.* 8:2042 (Oct. 29) 1929.

22. The inequalities of the first sound, which occur in extrasystolic and auricular fibrillation, are easily differentiated. In these conditions the variations are noted in connection with ventricular irregularity.

Book Reviews

TREATMENT IN GENERAL PRACTICE. By HARRY BECKMAN, M.D., Professor of Pharmacology and Therapeutics, Marquette University Medical School. Price, \$10. Pp. 899. Philadelphia: W. B. Saunders Company, 1930.

This book is a comprehensive treatise of therapy written by a teacher of pharmacology and therapeutics for the student and general practitioner of medicine. The author feels that, with few notable exceptions, the teaching of therapeutics is more or less neglected, usually consisting of a formal course of lectures to junior students, supplemented later by what little instruction may be given to senior students during hours in the clinic in the various departments. The latter is usually rather sketchy "simply because in the (teacher's) immersion in the task of acquainting the student with the prodigious methodology of modern diagnosis, no time is left for an exhaustive consideration of the treatment of disease."

The book has been carefully edited, is printed in clear type on good paper and is arranged by systems, i. e., infectious and parasitic diseases, constitutional diseases such as allergy, deficiency diseases and metabolic disorders, diseases of the gastro-intestinal tract, the respiratory, excretory, circulatory and nervous systems and the integument, followed by a consideration of drug addiction, poisons, burns, obstetrics and miscellany.

To quote from the preface, "Therapy has been evolved out of the experience of physicians all over the world. The true authors of the book, then, are those men and women whose names appear in the Bibliography. Whenever possible, I have presented their work in their own words, but often it has been necessary to abstract and condense. . . ." Each disease condition is defined, and there is a brief statement of the etiology, symptomatology and usual course, followed by a thorough discussion of therapy and prophylaxis. There are numerous prescriptions and tables, an extensive bibliography and an index. This treatise should prove a valuable aid to the student and practitioner.

both cases the curves showed similar time relations. In one, inequalities in amplitude seemed to vary from day to day, and occasionally no differences could be recorded. In three other cases tracings of the pulse waves failed to reveal changes in the amplitude of the waves that could be related to the auriculoventricular intervals.

4. Simultaneous records of changes in the intensity of sound and amplitude of the pulse waves showed that either comparatively loud or faint sounds may be associated with comparatively large or small pulse waves. It was therefore concluded that while both types of changes were dependent on phenomena resulting from auricular systole, the factors concerned were not identical.

5. It is suggested, principally on the basis of work by Wiggers and by Gesell and some indirect evidence obtained by us, that the changes observed in the amplitude of the pulse waves are due principally to the effects of auricular systole on ventricular filling and initial tension.

6. The provisional hypothesis is adopted that inequalities of the first heart sound observed are due principally to variation in the position of the mitral leaflets at the beginning of ventricular contraction.

7. The data presented indicate that in the clinical evaluation of the first heart sound as evidence of cardiac vigor, modifications dependent on the duration of the auriculoventricular interval should be discounted.

Prof. Charles Weyl of the Moore School of Electrical Engineering of the University of Pennsylvania constructed the three stage transformer coupled amplifier.

INDEX TO VOLUME 46

	PAGE		PAGE
BOOK REVIEWS—Continued		Colds, frequent chest colds; variability in their occurrence and bacteriology in those very susceptible to this type of cold	1
Hipertension Arterial: Hipertonía arterial o hiperplasia y los estados hipertensivos hipertónicos o de hiperplasia; M. R. Castex	161	Colitis, serum treatment for chronic ulcerative colitis.....	1039
Hypertension and Nephritis; A. B. Fishberg	358	Colon, reflex influence of colon, appendix and gallbladder on stomach.....	988
Praktische Differentialdiagnostik für Aerzte und Studierende. Herausgegeben von G. Honigmann. Band III. Differentialdiagnostik in der Psychiatrie; H. Haymann	552	Conception, does climate affect human conception rate?.....	921
Síndrome de Oclusión Coronaria; Battro..	899	Connery, J. E.: Correlation of Widal's post-digestive leukopenia as test for liver function with normal rhythm of leukocytes	1018
Some Aspects of the Cancer Problem; W. B. Bell	898	Corrosive Poisoning: See Mercuric chloride	
Symptoms of Visceral Disease. A Study of the Vegetative Nervous System in Its Relationship to Clinical Medicine; F. M. Pottenger.....	899	Daland, G. A.: Life of reticulocytes; experiments on their maturation.....	553
Three Minute Medicine. A Series of Brief Essays on Popular Medicine; L. R. Effler	164	Metabolism of normal and leukemic leukocytes	46
Treatment in General Practice; H. Beckman	1072	Dalton, J. B.: Diffusible calcium and proteins of blood serum in malignant disease	67
Urticaire; E. Joltrain.....	900	Dameshek, W.: Acute monocytic (histiocytic) leukemia, review of literature and case reports.....	718
Verhandlungen der deutschen Gesellschaft für Kreislaufforschung; II. Tagung. Herausgegeben von Prof. Dr. Bruno Kisch	164	Davison, C.: Primary carcinoma of lungs with metastases to central nervous system	680
Brice, A. T., Jr.: Boltz test in urinalysis..	778	Dextrose, modification of dextrose tolerance test as index of metabolic activity of liver	482
Brown, G. E.: Peripheral arterial disease in polycythemia vera.....	705	Diabetes Mellitus, colloid osmotic pressure of blood in.....	752
Buliowa, J. G. M.: Fatal human anaphylactic shock; report of case with autopsy findings and review of literature.....	306	is climate a responsible factor in etiology?	569
Burnham, L.: Transfusion from a group II (a) donor to a group III (b) recipient without fatal result.....	502	sugar consumption in its etiology.....	582
Byrd, H.: Sphenopalatine phenomena; present status of knowledge.....	1026	Digestion; efficiency with various foods and under various conditions.....	361
Byrd, W.: Sphenopalatine phenomena; present status of knowledge.....	1026	Diphtheria, hazard of incision for apparent quinsy in diphtheria.....	402
Calcium, diffusible calcium and proteins of blood serum in malignant disease.....	67	Doll, B. T.: Intermediate metabolism of foreign sugars.....	321
diffusible calcium of blood serum in allergic diseases.....	72	Dorsey, A. H. E.: Chronic arthritis; bacteriology of affected tissues.....	121
Cancer, carcinomatous degeneration of polyp of stomach; report of 3 personal cases with review of 24 recorded by others..	841	Duodenal Ulcer: See Peptic ulcer	
diffusible calcium and proteins of blood serum in malignant disease.....	67	Dwyer, H. V.: Peripheral neuritis complicated by massive collapse of lung following tonsillectomy.....	833
primary carcinoma of lungs with metastases to central nervous system.....	680	Electrocardiogram: See under Heart	
primary, of liver.....	105	Eliason, E. I.: Carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others.....	841
Cardiovascular disease; differentiation and diagnosis of certain ophthalmoscopic pictures in hypertensive diseases.....	901	Endocrine glands, diagnostic value of sugar tolerance curve in endocrinopathies...	984
Childrey, J. H.: Digestion; efficiency with various foods and under various conditions	361	Enema, evaluation of expulsion of enemas as a criterion of intestinal obstruction..	669
Chung, H. L.: Antibody formation in kala-azar	782	Epigastric pulsation; classification in regard to form of epigastriogram.....	333
Clarke, N. E.: Postoperative results in toxic goiter.....	266	Epilepsy, laboratory studies in.....	180
Climate, does climate affect human conception rate?	921	Erythrocyte sedimentation test in tuberculosis, study of 2,000 cases.....	787
geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris	741	red blood cell size in anemia; its value in differential diagnosis.....	440
Cohen, S. J.: Neutral red test in pernicious anemia	979	Exercise, after-effect of muscular exercise on production of basal heat; metabolism of obesity.....	40

INDEX TO VOLUME 46

Book Reviews are grouped together and are indexed under that heading in alphabetical order, under the letter B.

	PAGE
Addison's Disease, geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris.....	741
in a Negro, report of a case.....	375
Adkinson, J.: Frequent chest colds, variability in their occurrence and bacteriology of those very susceptible to this type of cold.....	1
Allergy: See Anaphylaxis and Allergy	
Althausen, T. L.: Modification of dextrose tolerance test as an index of metabolic activity of liver.....	482
Alvarez, W. C.: Blood pressure in 6000 prisoners and 400 prison guards.....	17
digestion; efficiency with various foods and under various conditions.....	361
Amyloidosis, relation of lipoid nephrosis to	137
Anaphylaxis and allergy: diffusible calcium of blood serum in allergic diseases....	72
fatal human anaphylactic shock with autopsy findings and review of literature	306
Andersch, M.: Metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight....	1002
Anderson, S. V.: Erythrocyte sedimentation test in tuberculosis, study of 2000 cases	787
Anemia, iron metabolism in pernicious and in secondary anemia.....	458
pernicious, blood regeneration during early remission	417
pernicious, geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris.....	741
pernicious, neutral red test in.....	979
red blood cell size in anemia; its value in differential diagnosis.....	440
Angina pectoris, geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris.....	741
Appendix, reflex influence of colon, appendix, and gallbladder on stomach.....	988
Artery, coronary, appearance time of T wave changes in electrocardiogram following acute coronary occlusion, reports of 2 cases	657
Arthritis, chronic; bacteriology of affected tissues	121
Asthma, bronchial, severe chronic intractable type.....	218
Bannick, E. G.: Action and excretion of nitrates	797
Banyl, A. L.: Erythrocyte sedimentation test in tuberculosis, study of 2,000 cases	787
Bargen, J. A.: Serum treatment for chronic ulcerative colitis.....	1039

	PAGE
Baumgartner, E. A.: Tropical sprue; experience with 36 cases.....	597
Beard, M.: Diabetes mellitus; colloidal osmotic pressure of blood.....	752
Bile salts, specific effect of bile salts on pneumococci and on pneumococcus pneumonia	644
Black, I.: Postoperative results in toxic goiter	266
Blood: See also Erythrocytes; Leukocytes chemistry, postmortem, in renal disease..	283
colloidal osmotic pressure of blood and diabetes mellitus.....	752
diffusible calcium and proteins of blood serum in malignant disease.....	67
diffusible calcium of blood serum in allergic diseases.....	72
nonprotein nitrogenous constituents in...	290
oxygen and carbon dioxide content of blood from internal jugular and other veins	630
plasma proteins.....	236
platelets, an improved indirect method for their enumeration.....	585
pressure, high, differentiation and diagnosis of certain ophthalmoscopic pictures in hypertensive disease.....	901
pressure, high, evaluation of prognosis..	227
pressure, high; so-called malignant hypertension, clinical and morphologic study	75
pressure in 6000 prisoners and 400 prison guards	17
sugar, arteriovenous difference in blood sugar content.....	605
sugar, diagnostic value of sugar tolerance curve in endocrinopathies.....	984
sugar; intermediate metabolism of foreign sugars	321
transfusion from a group II (a) donor to a group III (b) recipient without fatal result	502
Boikan, W. S.: Gastric sequelae of corrosive poisoning.....	342
Boltz test in urinalysis.....	778
Bone changes and parathyroid tumor.....	506
BOOK REVIEWS:	
Basis of epilepsy; E. Tracy.....	900
Baby's First Two Years; R. M. Smith...	360
Chest, (The); L. R. Sante.....	552
Clinical Examination of Nervous System; G. H. Monro-Krohn.....	900
Diagnostische und Therapeutische Irrtümer und deren Verhütung—Innere Medizin; Erstes Heft, Krankheiten des Stoffwechsels; S. Isaac.....	360
Die Arten der Schlaganfälle des Gehirns und ihre Entstehung; P. Schwartz.....	900
Edema and Its Treatment; H. Elwyn.....	162
Essentials of Medical Diagnosis; T. Horder and A. E. Gow.....	163
Handbuch der Ernährungslehre, Band II: Spezielle Diätetik der Krankheiten des Verdauungsapparates. Teil 1: Magen; C. von Noorden.....	360

INDEX TO VOLUME 46

	PAGE		PAGE
Lederer, M.: Postmortem blood chemistry in renal disease.....	283	Mills, C. A.: Diabetes mellitus. Is climate a responsible factor in etiology?.....	569
Leishmaniasis, antibody formation in kala-azar	782	Diabetes mellitus, sugar consumption in its etiology.....	582
Lennox, W. G.: Oxygen and carbon dioxide content of blood from internal jugular and other veins.....	630	Does climate affect human conception rate?	921
* Leukemia, acute monocytic (histiocytic) leukemia, review of literature and case reports	718	Geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris.....	741
Leukocytes, metabolism of normal and leukemic leukocytes.....	46	Morrell, C. A.: Chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys	382
Leukopenia, correlation of Widal's post-digestive leukopenia as test for liver function with normal rhythm of leukocytes	1018	Chemistry and metabolism in experimental yellow fever in Macacus rhesus monkeys; concentration of nonprotein nitrogenous constituents in blood.....	290
Lipoid nephrosis, pathology, genesis and relation to amyloidosis.....	137	Morris, A. E.: Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter	946
Liver, carcinoma of, primary.....	105	Moschcowitz, E.: Nature of Graves' disease	610
function, correlation of Widal's post-digestive leukopenia as test for liver function with normal rhythm of leukocytes	1018	Murphy, F. D.: So-called malignant hypertension; clinical and morphologic study	75
modification of dextrose tolerance test as index of metabolic activity of liver....	482	Murphy, W. P.: Red blood cell size and anemia; its value in differential diagnosis	440
Lung, peripheral neuritis complicated by massive collapse of lung following tonsillectomy	833	Myxedema, low basal metabolism without..	879
primary carcinoma of lungs with metastases to central nervous system.....	680	Negro, Addison's disease in a Negro, report of case.....	375
Mann, F. C.: Digestion: efficiency with various foods and under various conditions	361	Nephrosis: See under Kidney	
Margolles, A.: Influence of auricular contraction on first heart sound and radial pulse	1048	Neuritis, peripheral neuritis complicated by massive collapse of lung following tonsillectomy	833
Margolis, H. M.: Chronic arthritis; bacteriology of affected tissues.....	121	Nitrates, action and excretion of.....	797
Matzner, M. J.: Neutral red test in pernicious anemia.....	979	Novasurol: See Merbaphen	
Meckel's Ganglion: See Sphenopalatine ganglion		Obesity, metabolism of obesity; after-effect of muscular exercise on production of basal heat.....	40
Merbaphen, renal damage following administration of merbaphen (novasurol).....	494	metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....	1002
Mercuric chloride poisoning, gastric sequelae of.....	342	Olef, I.: Blood platelets; improved indirect method for their enumeration.....	585
Metabolism, basal; influence of special breakfast on basal metabolism of patients with pathologic condition.....	316	Ophthalmoscopic pictures in hypertensive diseases	901
in experimental yellow fever.....	290	Oppenheimer, B. S.: Differentiation and significance of certain ophthalmoscopic pictures in hypertensive diseases.....	901
intermediate of foreign sugars.....	321	Palmer, W. L.: Value of acid neutralization in treatment of gastric and duodenal ulcers	165
low basal metabolism without myxedema..	879	Parathyroid tumor and changes of bones...	506
of normal and leukemic leukocytes.....	46	Pardee, H. E. B.: Significance of electrocardiogram with a large Q in lead 3....	470
of obesity; after-effect of muscular exercise on production of basal heat.....	40	Peptic ulcer, effects of intravenous injections of foreign protein on peptic ulcer. experimental gastric ulcer; effect of consistency of diet on healing.....	768
of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....	1002	value of acid neutralization in treatment of gastric and duodenal ulcers.....	165
Meyer, J.: Effects of intravenous injections of foreign protein on peptic ulcer....	768	Peritoneum, demonstration of local immunity of peritoneum by means of Shwartzman phenomenon.....	410
Miller, G. H.: Reflex influence of colon, appendix and gallbladder on stomach..	988	Perspiration: See Sweat and sweat glands	
Miller, T. G.: Carcinomatous degeneration of polyp of stomach; report of 8 personal cases with a review of 24 recorded by others.....	841	Plitts, H. H.: Primary carcinoma of liver..	105

INDEX TO VOLUME 46

	PAGE		PAGE
Fasting, G. F. C.: Serum treatment for chronic ulcerative colitis.....	1039	Heart, appearance time of T wave changes in electrocardiogram following acute coronary occlusion; report of 2 cases..	657
Fauley, G. B.: Experimental gastric ulcer; effect of consistency of diet on healing	524	influence of auricular contraction on first heart sound and radial pulse.....	1048
Felsen, J.: Laboratory studies in epilepsy..	180	resuscitation of stopped heart by intracardiac therapy.....	553
Fishberg, A. M.: Differentiation and significance of certain ophthalmoscopic pictures in hypertensive diseases.....	901	significance of electrocardiogram with large Q in lead 3.....	470
Fishberg, E. H.: Intermediate metabolism of foreign sugars.....	321	Heath, C. W.: The life of reticulocytes; experiments on their maturation.....	533
Fitzhugh, G.: Red blood cell size in anemia, its value in differential diagnosis.....	440	Hershey, E.: Postmortem blood chemistry in renal disease	283
Frisch, I. A.: Demonstration of local immunity of peritoneum by means of Shwartzman phenomenon.....	410	Horwitz, W. A.: Primary carcinoma of lungs with metastases to central nervous system	680
Fukui, N.: Epigastric pulsation; classification in regard to form of epigastriogram	333	Hubbard, R. S.: Alkaline tide as method of studying gastric acidity.....	994
Gallbladder, reflex influence of colon, appendix and gallbladder on stomach.....	988	Hurxthal, L. M.: Appearance time of T wave changes in electrocardiogram following acute coronary occlusion, report of 2 cases.....	657
Gastric Ulcer: See Peptic ulcer		Hyman, A. S.: Resuscitation of stopped heart by intracardiac therapy.....	553
Giffin, H. Z.: Peripheral arterial disease in polycythemia vera.....	705	Hyperglycemia: See Blood, sugar	
Glassberg, B. Y.: Arteriovenous difference in blood sugar content.....	605	Hypertension, Arterial: See Blood pressure, high	
Diagnostic value of sugar tolerance curve in endocrinopathies.....	984	Immunity, demonstration of local immunity of peritoneum by means of Shwartzman phenomenon.....	410
Glover, E. C.: Metabolism of normal and leukemic leukocytes.....	46	Injection, intracardiac, resuscitation of stopped heart by intracardiac therapy	553
Goehl, R. O.: Evaluation of expulsion of enemas as criterion of intestinal obstruction	669	Intestine, obstruction; evaluation of expulsion of enemas as a criterion of intestinal obstruction.....	669
Goiter, exophthalmic; geographic or climatic variations in death rate from pernicious anemia, exophthalmic goiter, Addison's disease and angina pectoris..	741	Iron metabolism in pernicious and in secondary anemia.....	458
exophthalmic, nature of Graves' disease	610	Ivy, A. C.: Experimental gastric ulcer; effect of consistency of diet on healing....	524
exophthalmic, thyrotoxicosis following subtotal thyroidectomy for.....	946	Jacobi, M.: Addison's disease in a Negro, report of a case.....	375
toxic, postoperative results.....	266	Fatal human anaphylactic shock, report of case with autopsy findings and review of literature.....	306
Goodman, M.: Correlation of Widal's post-digestive leukopenia as test for liver function with normal rhythm of leukocytes	1018	Jewett, C. H.: Tropical sprue; experience with 36 cases.....	597
Gordon, J. E.: Hazard of incision for apparent quinsy in diphtheria.....	402	Kahn, I. S.: Bronchial asthma, severe chronic intractable type.....	218
Graves' Disease: See Goiter, exophthalmic		Kala-Azar: See Leishmaniasis	
Gray, I.: Neutral red test in pernicious anemia	979	Kartoon, L. B.: Effects of intravenous injections of foreign protein on peptic ulcer	768
Greenberg, D. M.: Diffusible calcium and proteins of blood serum in malignant disease	67	Kelth, N. M.: Action and excretion of nitrates	797
Diffusible calcium of blood serum in allergic diseases.....	72	Kerr, W. J.: Modification of dextrose tolerance test as index of metabolic activity of liver.....	482
Grill, J.: So-called malignant hypertension; clinical and morphologic study.....	75	Kidney disease, postmortem blood chemistry in.....	283
Gunther, L.: Diffusible calcium and proteins of blood serum in malignant disease	67	lipoid nephrosis, pathology, genesis and relation to amyloidosis.....	137
Diffusible calcium of blood serum in allergic diseases.....	72	ophthalmoscopic pictures in hypertensive diseases	901
Modification of dextrose tolerance test as an index of metabolic activity of liver	482		
Hawks, J. E.: Influence of special breakfast on basal metabolism of patients with pathologic condition.....	316	Lagen, J. B.: Modification of dextrose tolerance test as index of metabolic activity of liver.....	482

INDEX TO VOLUME 46

	PAGE		PAGE
van Leeuwen, W. S.: Pulmonary tuberculosis; treatment in allergen-proof chambers	637	Wangensteen, O. H.: Evaluation of expulsion of cnemas as a criterion of intestinal obstruction.....	669
Vital Capacity in college women; standards for normal vital capacity in college women	930	Whelan, M.: Action and excretion of nitrates	797
in college women; study of students with high and low vital capacity.....	938	Wicner, H. J.: Plasma proteins.....	236
Wakeman, A. M.: Chemistry and metabolism in experimental yellow fever in <i>Macacus rhesus</i> monkeys.....	382	Wiener, R. E.: Plasma proteins.....	236
Chemistry and metabolism in experimental yellow fever in <i>Macacus rhesus</i> monkeys; concentration of nonprotein nitrogenous constituents in blood.....	290	Wolferth, C. C.: Influence of auricular contraction on first heart sound and radial pulse	1048
Walker, I. C.: Frequent chest colds, variability of their occurrence and bacteriology in those very susceptible to this type of cold.....	1	Wright, V. W. M.: Carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others.....	841
Wang, C. C.: Influence of special breakfast on basal metabolism of patients with pathologic condition.....	316	Yellow fever, chemistry and metabolism in experimental yellow fever in <i>Macacus rhesus</i> monkeys.....	382
Metabolism of obesity; after-effect of muscular exercise on production of basal heat	40	chemistry and metabolism in experimental yellow fever in <i>Macacus rhesus</i> monkeys; concentration of nonprotein nitrogenous constituents of blood.....	290
Metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....	1002	Young, D. C.: Hazard of incision for apparent quinsy in diphtheria.....	402
		Ziegler, E. E.: Specific effect of bile salts on pneumococci and on pneumococcus pneumonia	644

INDEX TO VOLUME 46

	PAGE		PAGE
Pneumococci and pneumococcus pneumonia, specific effect of bile salts on.....	644	Sprunt, D. H.: Renal damage following administration of merbaphen (novasulrol)	494
Pneumonia, specific effect of bile salts on pneumococci and on pneumococcus pneumonia	644	Stanley, L. L.: Blood pressure in 6,000 prisoners and 400 prison guards.....	17
Polayes, S. H.: Postmortem blood chemistry in renal disease.....	283	Stieglitz, E. J.: Arterial hypertension, evaluation of prognosis.....	227
Polycythemia vera, peripheral arterial disease in.....	705	Stomach acidity, alkaline tide as method of studying gastric acidity.....	994
Polyp, carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others...	841	carcinomatous degeneration of polyp of stomach; report of 8 personal cases with review of 24 recorded by others.....	841
Proteins, diffusible calcium and proteins of blood serum in malignant disease.....	67	experimental gastric ulcer; effect of consistency of diet on healing.....	524
effects of intravenous injections of foreign protein on peptic ulcer.....	768	function, neutral red test in pernicious anemia	979
plasma	236	reflex influence of colon, appendix and gallbladder on stomach.....	988
Pulsation, epigastric; classification in regard to form of epigastriogram.....	333	Ulcer: See Peptic ulcer	
Quinsy: See Tonsillitis		Strong, G. F.: Primary carcinoma of liver..	105
Rabinowitch, I. M.: Diabetes mellitus; colloidal osmotic pressure of blood.....	752	Strouse, S.: Metabolism of obesity; after-effect of muscular exercise on production of basal heat.....	40
Origin of urobilinogen; a clinical experiment	1014	Metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....	1002
Reimann, H. A.: Antibody formation in kala-azar	782	Sugars, foreign, intermediate metabolism of.	321
Respiratory tract; frequent chest colds; variability in their occurrence and bacteriology in those very susceptible to this type of cold.....	1	Sweat and sweat glands; metabolism of obesity; basal metabolism and insensible perspiration during a period of reducing weight.....	1002
Reticulocytes; life of reticulocytes; experiments on their maturation.....	533	Thompson, P. K.: Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter.....	946
Retina in hypertensive diseases.....	901	Thompson, W. O.: Low basal metabolism without myxedema.....	879
Riddle, M. C.: Pernicious anemia; blood-regeneration during early remission....	417	Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter.....	946
Riecker, H. H.: Iron metabolism in pernicious and in secondary anemia.....	458	Thrush: See Sprue	
Rosenow, E. C.: Scrum treatment for chronic ulcerative colitis.....	1039	Thurmon, F. M.: Low basal metabolism without myxedema.....	879
Sala, A. M.: Addison's disease in Negro, report of a case.....	375	Thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter.....	946
Schmitz, H. L.: Metabolism of normal and leukemic leukocytes.....	46	Tonsillectomy, peripheral neuritis complicated by massive collapse of lung following tonsillectomy.....	833
Senior, F. A. (Mrs.): Does climate affect human conception rate?.....	921	Tonsillitis, hazard of incision for apparent quinsy in diphtheria.....	402
Shapiro, P. F.: Lipoid nephrosis; pathology, genesis and relation to amyloidosis	137	Tuberculosis, erythrocyte sedimentation test in, study of 2,000 cases.....	787
Shwartzman phenomenon, demonstration of local immunity of peritoneum by means of	410	pulmonary, treatment in allergen-proof chambers	637
Singer, H. A.: Gastric sequelae of corrosive poisoning	342	Tumor, parathyroid tumor and changes of bones	506
Smith, E.: Metabolism of obesity; after-effect of muscular exercise on production of basal diet.....	40	Turner, A. H.: Vital capacity in college women; standards for normal vital capacity in college women.....	930
Smith, F. M.: Reflex influence of colon, appendix and gallbladder on stomach.....	988	Vital capacity in college women; study of students with high and low vital capacity	938
Snapper, I.: Parathyroid tumor and changes of bones	506	Ulcer, Gastric: See Peptic Ulcer	
Sphenopalatine phenomena; present status of knowledge	1026	Urine, alkaline tide as method of studying gastric acidity.....	994
Sprue, tropical sprue, experience with 36 cases	597	Boltz test in urinalysis.....	778
		Urobilinogen, origin of; a clinical experiment	1014

